PREDICTORS OF PROSTATE CANCER OUTCOMES IN SASKATCHEWAN

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ABSTRACT

Background: Prostate cancer (PCa) is one of the leading causes of cancer mortality and incidence in Canada. Saskatchewan has one of highest mortality and incidence rates in Canada, and this doctoral research explores possible reasons for the higher mortality and incidence rates in Saskatchewan compared to the other provinces. While reasons for these PCa outcomes are not known, we hypothesize healthcare access factors may influence PCa outcomes, including PCa incidence, treatment usage and time trends in Saskatchewan, and we hypothesize additional factors may affect PCa treatment decision-making. To explore these hypotheses, in this dissertation we study the following research questions: (1) "Is the PCa incidence in Saskatchewan affected by changes in family physician density, the remoteness level of where a patient lives, and the closest PCa assessment centre from where a patient lives?"; (2) "Are the PCa treatment utilization rates in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?"; (3) "Are the PCa time-to-treatment outcomes in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?"; and (4) "What factors and corresponding themes in the literature have been identified to affect the treatment decision-making of localized prostate cancer patients in Canada and the United States?".

Methods: To explore research questions one, two, and three, we used data from: (1) Saskatchewan Cancer Registry, (2) Statistics Canada's Index of Remoteness, (3) Canadian Medical Association, and (4) Saskatchewan Covered Population. To explore research question four, we used data from: (1) MEDLINE, (2) EMBASE, (3) CINAHL, (4) AMED and (5) PsycInfo. For our first research question, we estimated the standardized incidence ratios (SIRs) of PCa and their associations with family physician density, remoteness level of where a patient lives and closest PCa assessment centre from where a patient lives in Saskatchewan using the Besag, York and Mollie (BYM) Bayesian method. For our second research question, we built multilevel generalized linear models to estimate the relationship between treatment choice and factors including remoteness level of where a patient lives and closest PCa assessment centre from where a patient lives. For our third research question, we conducted multivariable analysis to assess whether remoteness level of where a patient lives and closest PCa assessment centre from where a patient lives are associated with PCa time-to-treatment outcomes. For our fourth

research question, we conducted a scoping review using the process of Arksey and O'Malley to identify key factors commonly studied in localized PCa treatment decision-making.

Results: Family physician density was negatively associated with SIRs of metastatic PCa (IRR = 0.935; 95% CrI: 0.880 to 0.998]) and SIR of high-risk PCa (IRR = 0.927 ; 95% CrI: 0.880 to 0.975). We found that patients living in the rural areas have lower odds (OR = 0.59; 95% CI: 0.45 to 0.77; P < .001) of having surgery compared to patients living in the greater urban areas. RT diagnosis-to-treatment time was positively correlated with the remoteness-index (IRR = 1.45; 95% CI: 1.21 to 1.75; P < .001). Five themes in localized PCa treatment decision-making were identified: treatment type, socioeconomic characteristics, personal reasons, psychological experience, and involvement in the decision-making process.

Conclusions: Healthcare access factors were associated with PCa incidence, treatment choice and treatment delays in Saskatchewan. We found family physician density was negatively associated with incidence of high risk and metastatic PCa. There were regional disparities in PCa treatment choice and residents living in rural/remote areas were associated with delays for PCa treatment. We found five key factors associated with PCa treatment decision-making. This work informs future research and cancer care practices and policies to improve PCa patient outcomes in Saskatchewan and Canada.

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To my parents and siblings who shaped me to be my best.

To Pallavi for always believing in me.

To Idreys.

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LIST OF ABBREVIATIONS

AIC	Akaike's Information Criterion
AS/WW	Active Surveillance/Watchful Waiting
BYM	Besag, York and Mollie
CAM	Complementary Alternative Medicine
CARO	Canadian Association of Radiation-Oncologists
CFPC	College of Family Physicians of Canada
CI	Confidence Interval
CMA	Census Metropolitan Area
CrI	Credible Interval
CMQ	Collège des médecins du Québec
CT	Chemotherapy
CTFPHC	Canadian Task Force on Preventive Health Care
DRE	Digital Rectal Exam
GA	Geographic Area
GUROC	Genito-Urinary Radiation Oncologists of Canada
HT	Hormonal Therapy
ICC	Intraclass correlation
IQR	Interquartile range
IRR	Incidence Rate Ratio
LPC	Localized Prostate Cancer
OR	Odds Ratio
PCa	Prostate Cancer
PCA	Principal Component Analysis
PSA	Prostate Specific Antigen
ROC	Receiving Operating Characteristic
RT	Radiation Therapy
RTTx	'Ready-to-treat'-to-treatment
SCP	Saskatchewan Covered Population
SCR	Saskatchewan Cancer Registry

SIR	Standardized Incidence Ratio
TNM	Tumor Node Metastasis
USPSTF	United States Preventative Service Task Force

CHAPTER 1 – INTRODUCTION

Prostate cancer (PCa) is the leading cause of cancer among Canadian men, accounting for 1 in 5 new cancer cases in Canada (1). In 2020, PCa was estimated to cause of third highest number of deaths from cancer among Canadian men (after lung and colorectal) (1). Based on the latest 2019 Canadian provincial estimates, Saskatchewan had the highest projected age-standardized mortality rate (29.8 deaths per 100,000) and third highest projected age-standardized incidence rate (117.8 cases per 100,000), compared to other provinces (2). This doctoral research explores possible reasons for the lower survival and higher mortality rates in Saskatchewan, when compared to other provinces.

To explore possible reasons for the Saskatchewan rates, first we need background information regarding diagnosis, classification, and treatment procedures for PCa. The first section in this chapter describes diagnosing PCa. The second section describes the classification of PCa that could influence treatments received by patients. The third section describes the treatments for PCa. The fourth section looks at how healthcare access in Saskatchewan affects diagnosis and treatment outcomes for PCa. The last sections in the chapter respectively provide the problem statement and study objectives/research questions for this doctoral research, and the references used throughout the chapter.

1.1. Diagnosis of PCa

The first step of PCa diagnosis involves two common methods of PCa screening: a digital rectal exam (DRE) and a prostate-specific antigen (PSA) test (3). The DRE screening method involves a physical examination where the size and consistency of the prostate gland are examined (3). The DRE focuses on identifying abnormalities (including indications of hard, nodular and irregular areas) during the examination of the prostate gland and the surrounding area (3). While about 1 in 4 abnormal DREs may be due to PCa, an abnormal DRE could be indicative of other cancers or prostate conditions (3). The second screening method is via a blood test identifying the concentration of a specific molecule produced by the prostate gland: the prostate-specific antigen (PSA) (4), because PCa can lead to elevated levels of PSA in the blood (5). The efficacy of using a PSA test to screen for PCa is compromised because several other conditions affecting the prostate gland (such as chronic prostatitis and benign prostatic

hypertrophy), can lead to elevated PSA levels in the blood (4). Consequently, screening for PCa via PSA testing (i.e., PSA screening) is a controversial topic. The poor sensitivity and specificity of PSA tests in detecting PCa and the overall harm-to-benefit ratio associated with early detection of PCa have led to mixed recommendations for PSA screening (5).

The Canadian Task Force on Preventive Health Care (CTFPHC) recommends against using PSA tests for PCa screening in all men (6). The United States Preventative Service Task Force (USPSTF) recommends PCa screening via PSA tests based on patient's preference among men who are 55 to 69 years old (7). The USPSTF also recommends that PCa screening via PSA tests should be based on family history, race/ethnicity, comorbid conditions, other identified health risks and patient preferences (7). The differing recommendations provided by the CTFPHC and USPSTF on PCa screening via PSA tests add to the challenge for healthcare providers on how to best approach PCa detection and diagnosis (8).

In spite of the challenges associated with using a DRE and a PSA test to diagnosis PCa, the diagnosis of PCa is initiated based on an abnormal DRE during physical examination and/or raised PSA levels (typically more than 4.0 ng/mL) in the blood sample (9). The confirmation of a PCa diagnosis is based on a prostate biopsy (9).

Studying PCa diagnosis patterns in a population assists in identifying if the cancer was detected early in prognosis or if there were any patterns of late detection. Diagnosis patterns for PCa could be assessed using incidence rate, which measures the number of newly diagnosed cases in each area or population over a specified period of time (10). Due to the high PCa incidence rate in Saskatchewan (as mentioned earlier), this thesis assesses PCa diagnosis patterns in Chapter 3 (2). Specifically, in Chapter 3 we study PCa diagnosis patterns in Saskatchewan, stratified by different classifications of PCa (with further details on classification of PCa being provided in the next section).

1.2. Classification of PCa

In men diagnosed with PCa, the biopsy is used to classify the PCa using clinical staging, anatomic staging, and risk levels. The clinical staging of PCa is based on the TNM (T=tumor, N=node, M=metastasis) staging system (9). The T, N and M stages respectively measure the size/extent of the tumor, spread of the tumor to any lymph nodes and spread of the tumor to

distant parts of the body (11). In the process of assigning an anatomic stage, a grading system called Gleason score is used, which involves assigning a score to the cancerous cells based on their appearance and behavior (9).

The TNM stage, Gleason score, and PSA levels are used to categorize the PCa into anatomic stages (using the American Joint Committee on Cancer staging, 7th Edition) (12). The anatomic stages include Stages I, IIA, IIB, III and IV (12). The TNM staging is also used to categorize PCa as localized, locally extensive and metastasized (9). PCa in patients with T1 or T2 T-stage with no spread to the lymph nodes or distant parts of the body is considered localized (9). PCa in patients with T3 or T4 T-stage with no spread of the tumor to the lymph nodes or distant parts of the body is considered locally extensive (9). PCa in patients at any T-stage where the tumor has spread to the lymph nodes or distant parts of the body is considered metastasized (9).

Table 1.1. Genitourinary Radiation Oncologists of Canada (GUROC) criteria for risk categories (13).

Risk Category	PSA Value	Gleason Score	Clinical T Stage
Low (must have all)	≤10 ng/mL	≤6	T1-T2a
Intermediate (must have all else low risk)	≤20 ng/mL	7	T1/T2
High (any one is sufficient)	>20 ng/mL	8-10	T3a-T4

PCa cases are also classified into risk levels. The risk levels are regarding PCa biochemical recurrence, where recurrence or relapse of PCa means the cancer has returned after it has been treated (14). After treatment if the only sign of recurrence is PSA elevation, then it is called biochemical recurrence (14). While a PSA ≥ 0.2 ng/dL is the commonly used definition, currently there is no consensus on a standard definition measuring biochemical recurrence among post-treatment PCa patients (15). The risk levels for PCa biochemical recurrence among non-metastasized PCa patients can be derived pre-treatment using the TNM stage, Gleason score and PSA levels (16, 17). These risk levels are assigned as low, intermediate or high and were developed by D'Amico *et al.* in 1998 (17). Since then, several modifications of these risk levels have been proposed and adopted by different organizations including the Genito-Urinary Radiation Oncologists of Canada (GUROC) (Table 1.1) (18). Since both D'Amico and GUROC

risk classifications are widely used as a tool by physicians for assisting patients in choosing appropriate treatments for PCa, in Chapter 3, 4, 5 and 6 we further considered D'Amico/GUROC risk classification when studying PCa outcomes. In this doctoral research, the term "outcomes" refers to PCa standardized incidence ratios in Chapter 3, PCa treatment choices in Chapter 4, PCa time-to-treatment results in Chapter 5 and PCa treatment decision-making themes in Chapter 6.

1.3. Treatments for PCa

The appropriate treatment for PCa depends on several factors including the risk level, TNM stage, Gleason score, treatment side effects, age, life expectancy, comorbidity and patient preferences (19). There are four general treatment options for localized (see section 1.2 for definition) PCa: active surveillance/watchful waiting, prostatectomy or surgery, radiation therapy, and hormonal therapy (19). For locally extensive and metastasized PCa, the treatment options could be a combination of surgery, radiation therapy, hormonal therapy and chemotherapy (19). In Canada, the most commonly used PCa treatments vary between provinces (13). For surgery, beside provincial variations in the usage, rates of use also depend on the PCa risk level (with the highest rates among intermediate-risk) and the age of the patient (with the lowest rates among patients over the age of 75) (13). Among high-risk PCa patients, radiation therapy is the most common treatment (13). In Canada, PCa treatment statistics for active surveillance/watchful waiting and hormonal therapy (similar to what is described for surgery and radiation therapy earlier) are not available (13). These commonly used treatments described above are available in Saskatchewan, including active surveillance/watchful waiting, surgery, radiation therapy and hormonal therapy (20). In Saskatchewan, surgery and radiation therapy for PCa are available in two cities – Saskatoon and Regina (21, 22). Hence, the residents living outside of Saskatoon and Regina travel to receive their surgery or radiation therapy treatment. In Chapter 4 of this thesis, we study PCa treatment patterns in Saskatchewan.

Treatment patterns for PCa could be influenced by treatment decision-making factors including patient preferences (19). A recent report in Canada emphasized the need for prioritizing individual needs in the treatment decision making process (13). Treatment decision making can be facilitated using decision aids and other educational tools for patients (13).

Decision to choose a treatment may be influenced by the types of treatment side effects associated with a given treatment (23-29). Patients prefer a shared treatment decision making process with their healthcare provider (30). In this thesis, we further explore PCa decision making factors in Chapter 6.

Receiving timely treatment is also necessary to improve PCa patient outcomes (31-34). In Canada, wait times for PCa related surgeries are known to be longer than for surgeries for other major cancer types (breast, lung, colorectal and bladder) (35). In addition, wait times for surgery and radiation therapy vary between provinces (13). For patients, both the choice of, and timing for, PCa treatment can be influenced by the availability of, and access to, PCa treatments (36, 37). Availability and access are two of the five components that define healthcare access. Research shows how both of these components can influence one's PCa treatment choice (36-38). Since healthcare access factors may influence treatment outcomes, in Chapter 4 and 5 of this thesis, we explore treatment outcomes in Saskatchewan and their association (if any) with healthcare access factors. Further details on healthcare access are provided in the next section.

1.4. Healthcare Access

Healthcare access is defined as the fit between the patient and the health care system, that can be measured based on the following components: availability, accessibility, accommodation, affordability and acceptability (38). Availability refers to the adequacy of the resources (e.g., number of physicians, facilities, etc.) to meet the patient demands; accessibility refers to the role of geography (e.g., distance, travel, time) when a patient is seeking healthcare; accommodation refers to the structure (e.g., hours of operation, wait-time) of the healthcare system that addresses patients and their needs appropriately; affordability is the role of finance (e.g., insurance, income, ability to pay) when a patient is seeking healthcare; and acceptability is the role of attitude (e.g., patient or provider's age, sex, ethnicity, cultural responsiveness) when a patient is seeking healthcare (38).

In the literature, the components of healthcare access are associated with various PCa outcomes (39-42). For example, in terms of the availability component of healthcare access, research from the United States shows that there is an association between the number of urologists in a geographic area and PCa mortality rates (a negative correlation) (39). In terms of

accessibility, one study found factors, including higher incomes and living in rural areas, influence how much people are willing to travel for PCa radiation treatment to larger and more established treatment locations (40). In terms of accommodation, a recent report shows nearly a third of PCa patients in Saskatchewan had to wait for their first consultation appointment without receiving any explanation for the delay, leading to frustration and anxiety (13). In terms of affordability, a study in the United States found uninsured PCa patients face treatment delays (41), which have been associated with adverse pathological outcomes (42). In Canada, PCa patients have reported lack of support in paying extra costs associated related to cancer care (13). In terms of acceptability, a Canadian report has emphasized the importance of patient-centred approaches in PCa care through communication, information sharing and shared-decision making with patients (13). The acceptability component includes cultural factors that may influence patient decision-making in seeking care (43). Culturally appropriate care is key to improving acceptability in the health system through addressing bias, discrimination and racism; expanding patient-centred approaches; and meeting the holistic care needs of patients (44). In Canada, the acceptability of the health services impacts the health outcomes of Indigenous peoples (44).

Returning our focus to Saskatchewan, healthcare access is known to be an issue in Saskatchewan (45, 46). Studies have found issues regarding healthcare provider availability, longer driving distances (accessibility), and concerns regarding wait-times (accommodation) (45, 46). There is no literature regarding whether healthcare access is affecting incidence and treatment rates among Saskatchewan PCa patients.

1.5. Research Gaps, Objectives and Questions

To our knowledge, no literature discusses the reasons for the high incidence and mortality rates in Saskatchewan, compared to other provinces. Specifically, there are no studies assessing associations (if any) between healthcare access factors in Saskatchewan and PCa incidence, treatment utilization and treatment delays. While the current literature on treatment decision-making studies focuses on factors for specific patient profiles, for example, ethnic and racial minorities, different age groups, and specific treatment options (23, 24, 26, 27, 47-50), we did

not find any literature that comprehensively identifies overarching themes regarding factors affecting localized PCa treatment decision-making.

Based on the research gaps identified in the previous sections, the objectives of this study are to:

1. determine the associations (if any) between components of healthcare access and each of PCa incidence, treatment usage and time-to-treatment trends among Saskatchewan patients; and
2. identify and describe the overarching themes influencing treatment decision-making for localized PCa patients.

To address Objective 1, we propose the following research questions: (1) "Is the PCa incidence in Saskatchewan affected by changes in family physician density, the remoteness level of where a patient lives, and the closest PCa assessment centre from where a patient lives?"; (2) "Are the PCa treatment utilization rates in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?"; and (3) "Are the PCa time-to-treatment outcomes in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?". To address Objective 2, we propose the research question: "What factors and corresponding themes in the literature have been identified to affect the treatment decision-making of localized prostate cancer patients in Canada and the United States?".

In this dissertation, we explore these four research questions. Chapter 2 (Methods) describes the data sources, data, and the study design used to study each research question. Chapter 3 explores Research Question 1 of Objective 1, where we identify clusters of higher and lower than expected PCa incidence in Saskatchewan, assess the effects that different healthcare access factors have on the estimated PCa incidence in Saskatchewan, and identify any geographical disparities in risk-stratified PCa incidence in Saskatchewan. Chapter 4 explores Research Question 2 of Objective 1, where we identify the possible relationship between one's initially-chosen PCa treatment and different healthcare access factors, and we identify any regional disparities in PCa treatment utilization. Chapter 5 explores Research Question 3 of Objective 1, where we assess the associations between time-to-treatment outcomes and different

healthcare access factors, and we identify possible regional disparities in PCa time-to-treatment outcomes. Chapter 6 explores Research Question 1 of Objective 2, where we systematically identify several factors affecting PCa treatment-decision-making in Canada and the United States. Chapter 7 concludes the doctoral research and identifies future areas of research exploration.

The University of Saskatchewan BioMedical Research Ethics Board provided ethics approval (Bio-REB certificate #15-34) for this doctoral research (Appendix A).

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CHAPTER 2 – METHODS

This chapter provides the data sources, data descriptions, and study design used to explore the two objectives for this research:

Objective 1: determine the associations (if any) between components of healthcare access and each of PCa incidence, treatment usage and time-to-treatment trends among Saskatchewan patients; and

Objective 2: identify and describe the overarching themes influencing treatment decision-making for localized PCa patients.

2.1. Data Sources

In this section, we first summarize the needed data sources and the data variables extracted from the data sources to address Objectives 1 and 2.

2.1.1. Data Sources to Study Objective 1

There were four data sources used to study Objective 1: (1) Saskatchewan Cancer Registry, (2) Statistics Canada's Index of Remoteness, (3) Canadian Medical Association's physician density, and (4) Government of Saskatchewan's Covered Population (1-4). This section describes each of these data sources and the data extracted from these sources.

2.1.1.1. The Saskatchewan Cancer Registry (SCR)

The Saskatchewan Cancer Registry (SCR) is a database of cancer health information for cancer patients diagnosed in Saskatchewan and is administered by the Saskatchewan Cancer Agency (1). The SCR consists of patient data on demographics, medical history, diagnostic findings, cancer information, cancer therapy, follow-up and death information (1). The SCR data obtained for this study consisted of information for 3,526 PCa patients diagnosed in Saskatchewan between 2010 and 2014. The SCR data consisted of following information on PCa patients: five-year age groups of patients (starting from age group of "35-39" till oldest age group of 90+; note age was not available as a continuous variable), diagnosis date (date PCa was diagnosed in the patient per the SCR), treatment types and dates (start date of treatments including chemotherapy, hormonal therapy, radiation therapy and surgery; ready to treat date for

radiation therapy), clinical staging information (PSA value, Gleason score, TNM-stage), and geographic locations of the patients. The SCR does not collect the treatment status of patients when their treatments were active surveillance/watchful waiting. Consequently, we assumed that patients in the SCR with no treatment status information were undergoing active surveillance/watchful waiting. For the geographic locations of the patients, the SCR categorized Saskatchewan communities in central and southern Saskatchewan into 82 geographic areas (GAs) using residence codes for privacy reasons (Figure 2.1) (4). Northern Saskatchewan could not be subdivided into smaller geographic areas due to privacy reasons. In addition, there were not enough data from northern Saskatchewan to allow statistical modelling (i.e., cell counts were less than 5 for the variables of interest). Hence, northern Saskatchewan was not included in any analyses.

2.1.1.2. Statistic Canada's Index of Remoteness

To quantify the remoteness of a geographical area, we derived the remoteness index for a GA using the Index of Remoteness developed by Statistics Canada for Canadian communities, because the Index of Remoteness accounts for the size of the population and proximity to all population centres (2). The values for Statistics Canada's Index of Remoteness range from 0 to 1 with higher values equating to higher remoteness levels (2).

2.1.1.3. Canadian Medical Association

Physician count data for the province of Saskatchewan were sourced from the Canadian Medical Association for the year 2011, because the 2011 data were the only available data for the time period between 2010 and 2014 (3). The retrieved data consisted of a count of family physicians and general practitioners licensed to practice medicine within Saskatchewan, and Canadian Medical Association provided the data using Statistics Canada's Census Subdivision geographic boundaries (5). The Canadian Medical Association sourced its information from The College of Family Physicians of Canada (CFPC), The Royal College of Physicians and Surgeons of Canada, individual Canadian Medical Association members and Collège des médecins du Québec (CMQ) (6-8). When determining physician counts, the Canadian Medical Association excluded retired physicians, physicians older than 80 (who were assumed retired), medical residents, medical students and anyone without a current valid mailing address.

2.1.1.4. Saskatchewan Covered Population

To generate standardized incidence ratios (SIRs) (mentioned in section 2.1.1.1), Saskatchewan Covered Population (SCP) data were used. The SCP is a count of eligible individuals with health insurance benefit in Saskatchewan (4). The SCP consists of all residents in Saskatchewan with exception of: (a) member of Canadian Forces, (b) inmates of federal prison, and (c) those who do not meet residency requirements for Saskatchewan (4). Because the overall SCP data deviated less than 3% each year between 2010 and 2014 (9), we chose to use the data from the midpoint year 2012 (between 2010 and 2014) to generate SIRs (10). Further details about SIRs are available in Chapter 3.

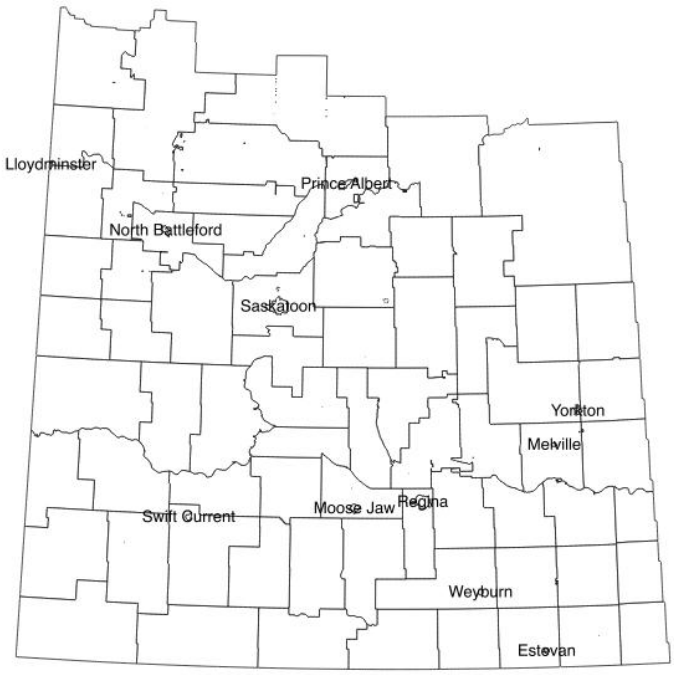

Figure 2.1: Defined geographic areas and major cities in the study sample in Saskatchewan.

2.1.2. Data Sources to Study Objective 2

There were five data sources to study Objective 2: (1) MEDLINE, (2) EMBASE, (3) CINAHL, (4) AMED and (5) PsycInfo. Data were compiled from each of the data sources using the inclusion and exclusion criteria described in Chapter 6.

2.1.2.1. MEDLINE

MEDLINE is a bibliographic database that contains references and journal articles in the life sciences (11).

2.1.2.2 EMBASE

Similar to MEDLINE, EMBASE is a bibliographic database that contains references and journal articles in the life sciences (12).

2.1.2.3. CINAHL

CINAHL is a bibliographic database that contains references and journal articles for nursing and allied professional, and includes topics on biomedicine and consumer health (13).

2.1.2.4. AMED

Allied and Complementary Medicine Database (AMED) is a bibliographic database that is designed for healthcare providers and focuses on alternative and allied therapies (14).

2.1.2.5. PsycInfo

PsycInfo is a bibliographic database that contains references and journal articles in behavioural and social science (15).

2.2. Research Question 1 of Objective 1

Our first research question to study Objective 1 was "Is the PCa incidence in Saskatchewan affected by changes in family physician density, the remoteness level of where a patient lives, and the closest PCa assessment centre from where a patient lives?". In this section, we first summarize the data used from the data sources and then the methodologies used to generate information to explore this question. Details for the complete study can be found in Chapter 3.

2.2.1. Data and Variables

For this study, data from four sources were used: (1) Saskatchewan Cancer Registry (SCR), (2) Statistics Canada's Remoteness of Index, (3) Canadian Medical Association, and (4) Saskatchewan Covered Population (all described in section 2.1.1). We used the SCP (section

2.1.1.4) data and PCa case counts per GA from the SCR to derive four outcome variables based on the GUROC risk levels: (1) low risk SIRs, (2) intermediate risk SIRs, (3) high risk SIRs and (4) metastatic SIRs. To compute a SIR for a GA for a specific outcome variable, the numerator was the number of associated PCa patients (i.e., patients with a particular GUROC level) in the GA and the denominator was the value from the Saskatchewan Covered Population data (section 2.1.1.4.) (full details can be found in Chapter 3).

The independent variables used in this study were closest PCa assessment centre to a GA, GA remoteness index, and physician density for a GA. For privacy reasons, the exact residence locations of the patients were not available, hence the data needed to calculate a patient's driving distances to different PCa assessment centres were not available. Consequently, we used the centroids of the GAs as the approximate location of where patients live within a GA and where treatment centres were located within a GA. Then the closest PCa assessment centre (as Regina or Saskatoon) to each GA was calculated based on the shortest Euclidean distance between the centroid of the GA and the centroids of Saskatoon and Regina. We derived the GA remoteness index as the average of the Statistics Canada Indices of Remoteness for the regions forming the GA (Figure 2.1) (2). To compute the physician density of a GA, we derived the numerator: physician count for a geographic area, to be the sum of the physician counts for the Census Subdivision areas forming the GA, and the denominator using Saskatchewan Covered Population data (section 2.1.1.4.) (details of the specific calculation can be found in Chapter 3).

2.2.2. Study Design

We used an ecological study design to address our research question, that is to assess if there were any associations between healthcare access factors (including closest PCa assessment centre to a GA, physician density and GA remoteness index) and PCa SIRs in Saskatchewan (16). For this study, we used SIRs to account for the varying population sizes of the GAs, and to identify areas with lower or higher than expected incidences of PCa for each risk levels. Given the nature of geographic data, the presence of spatial dependence in the PCa SIRs would violate the assumption of independence between the SIRs in a statistical analysis (17). To determine this, Global Moran's I statistics were used to identify the existence of any spatial dependence in the PCa SIRs (18). We also used exploratory spatial statistics, including the Local Moran's I and the Spatial Scan Statistics to identify clusters of higher than and lower than expected SIRs in

Saskatchewan (18-20). The Bayesian spatial analysis method introduced by Besag, York, and Mollie (BYM model) was used to account for any spatial dependence when assessing the associations (if any) between healthcare access factors and PCa SIRs (details for each of the statistical methods can be found in Chapter 3) (16, 21). The spatial smoothing of the PCa SIRs using the BYM method reduced the "noise" (i.e., large fluctuations) in the data while taking into account information from neighbouring GAs. Hence, the spatial smoothing of the PCa SIRs enhanced the process of identifying underlying patterns of PCa incidence in Saskatchewan (22).

An advantage of using an ecological study design is that it allows studying an area-level measurement (PCa incidence in a geographic area) that cannot be measured at an individual level (17). This methodology also allows the assessment of area-level exposures (healthcare access factors), including physician density, GA remoteness index and the closest PCa assessment centre to a GA. An advantage of using spatial analysis when assessing the association between PCa incidence and the healthcare access factors is that the estimated errors and statistical significance were adjusted for any spatial dependence (if it exists) (23). A strength of using Bayesian spatial methods is that it allows for estimating reliable disease rates in low population areas (given the low-density population of Saskatchewan) because of the flexibility of Bayesian models to account for uncertainties or biases due to possible spatial and non-spatial variations in the disease (22, 24-26). Hence, spatial analysis improved the estimated measures assessing association between PCa incidence and healthcare access factors.

2.3. Research Question 2 of Objective 1

Our second research question related to study Objective 1 was "Are the PCa treatment utilization rates in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?". Here we summarize the needed data, and then describe the methodologies used to generate information needed to explore this question. Details for the complete study can be found in Chapter 4.

2.3.1. Data and Variables

For this study, data from two data sources were used: (1) Saskatchewan Cancer Registry (SCR), and (2) Statistics Canada's Remoteness of Index (both described in section 2.1.1). Our outcome variables were based on a patient choosing a particular PCa treatment within 2-years of

PCa diagnosis, which was based on the Canadian Partnership Against Cancer definition (27). Treatment dates for each type of PCa treatment and PCa diagnosis dates were used to derive four outcome variables: surgery (yes/no), radiation therapy (yes/no), hormonal therapy (yes/no), and chemotherapy (yes/no) as follows. If a PCa patient had surgery within 2 years after PCa diagnosis, our surgery variable was assigned "Yes"; otherwise, it was assigned "No". The same process was used to derive our radiation therapy, hormonal therapy, and chemotherapy variables. A fifth outcome variable (active surveillance/watchful waiting) was derived with the value "Yes" if a patient did not undergo radiation therapy, hormonal therapy, surgery and chemotherapy within 2 years after PCa diagnosis, or "No" otherwise.

We used closest PCa assessment centre to a GA (section 2.2.1.) and GA remoteness index (section 2.2.1.) as the independent variables of interest. From Statistics Canada's Remoteness of Index data, we also derived an urban/rural categorical variable for each GA. The criteria for assigning urban/rural categories were based on the GA remoteness index ranges for census metropolitan areas and smaller areas (2). The GA remoteness index values less than 0.35 were categorized as "greater urban area" because, per Statistics Canada's remoteness index, all large cities in Canada (known as Census Metropolitan Areas) were in that range (2). The GA remoteness index values greater than 0.40 were categorized as "rural" because no city were in that range (2).

This study also accounted for other variables including age groups (<60, 60-69, 70-79, 80 or above) and year of diagnosis (2010, 2011, 2012, 2013, 2014) derived from the SCR data source using the age at diagnosis and date of diagnosis variables (section 2.1.1.), respectively. The study also accounted GUROC risk level derived (as described in Section 2.2.1.). For the study, we used all but the chemotherapy outcome variable (due to lack of data). Because patient level information on physician access was not available and we used patient level information for this study, we did not include physician access as one of the study variables. Further details regarding the study variables are provided in Chapter 4.

2.3.2. Study Design

Chapter 4 used a cross-sectional study design to assess if there was any association between the type of PCa treatment and the healthcare access factors: the geographic area in

which a patient lives and the GA remoteness index. A multilevel hierarchical modelling approach was used to fit hierarchical linearized regression models accounting for individual and community-level information to the data (17). Hence we fit hierarchical multilevel models to incorporate and investigate the effect of the geographical areas where patients live (a contextual community-level effect) associated with PCa treatment choices in Saskatchewan, while assessing the impact of demographic differences among patients: age, year of diagnosis, and GUROC risk level (individual-level effects) (details for each of the statistical methods can be found in Chapter 4).

The reason for fitting hierarchical multilevel models was due to the possible clustered-data structure that could result from patients living in the same geographic area possibly having correlated observations, which can violate the assumption of independence when conducting linearized regression analysis (17), and hierarchical multilevel modelling can account for any correlation or clustering within the data structure (17). Hence, the use of hierarchical multilevel modelling adjusted the standard errors and statistical significance when assessing the association between PCa treatment utilization and healthcare access factors (17).

2.4. Research Question 3 of Objective 1

Our third research question to study Objective 1 was "Are the PCa time-to-treatment outcomes in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?". Similar to previous sections, we first summarize the needed data and then describe the methodologies used to generate the information needed to explore this question. Details for the complete study can be found in Chapter 5.

2.4.1. Data and Variables

To address Research Question 3 of Objective 1, the outcome variables for this study were: (1) time from the PCa diagnosis date to the radiation therapy treatment date; and (2) time from the PCa "ready-to-treat" date to the radiation therapy treatment date. Both outcomes were derived using SCR data source using the PCa diagnosis date, radiation therapy "ready-to-treat" date, and radiation treatment date (section 2.1.1.). Only radiation therapy time-to-treatment outcomes were assessed because time-to-treatment data for other PCa treatments were not

available. The first outcome (time from PCa diagnosis to radiation therapy) was calculated as the difference between PCa diagnosis date and radiation therapy start date. The second outcome variable (time from PCa "ready to treat" to radiation therapy) was calculated as the difference between the PCa "ready to treat" date and the radiation therapy start date.

The variables of interest for the study were closest PCa assessment centre to a GA and GA remoteness index as derived in section 2.2.1. From Statistics Canada's Remoteness of Index data source, the chapter used the GA remoteness index variable to assess if any differences exist in PCa time-to-treatment outcomes among patients living in remote regions compared to urban areas. This study also accounted for other variables including age groups (<60, 60-69, 70-79, 80 or above), year of diagnosis (2010, 2011, 2012, 2013, 2014), GUROC risk level and number of treatments as derived in sections 2.1.1 and 2.2.1.

Similar to Chapter 4, since this chapter used patient level information, and patient level information on physician access was not available, this chapter was not able to assess physician access. Further details are available in Chapter 5.

2.4.2. Study Design

Chapter 5 used a cross-sectional design using secondary cancer registry data to assess if there were any associations between healthcare access factors (including geographic location where patient lives and GA remoteness index) and PCa time-to-treatment outcomes. First, this study assessed the associations between healthcare access factors and PCa time-to-treatment outcomes using non-parametric statistics (including Mann Whitney U two sample statistic and Kruskal-Wallis equality-of-population rank test). Median time-to-treatment estimates for PCa were readily available in the literature, and to provide comparable estimates to the literature, a median-based analysis was conducted (a median based analysis assesses the ranking of observations including the median to test differences between samples, unlike a parametric analysis which assesses the mean and variance of the samples) (28). In addition, due to the count nature of the outcomes, count regression modelling was used, controlling for age, year of diagnosis and GUROC risk level in the analysis (17). The count regression analysis included Poisson and zero-inflated negative binomial analyses (details for each of the statistical methods can be found in Chapter 5).

Multivariable regression analysis accounted for several factors or potential confounders (age, year of diagnosis, GUROC risk level) when assessing the association between time-to-treatment outcomes and healthcare access factors (17). Similar to Chapter 4, clustering within the data structure was also assessed. The zero-inflated negative binomial model accounted for the excess zero counts and over-dispersion in the time-to-treatment outcomes (17). Hence, the use of count regression models improved the estimation of any associations between PCa time-to-treatment outcomes and healthcare access factors.

2.5. Research Question 1 of Objective 2

Our research question to study Objective 2 was "What factors and corresponding themes in the literature have been identified to affect the treatment decision-making of localized prostate cancer patients in Canada and the United States?". In this section, we first summarize the data sources used to identify relevant literature, data collection process and then the methodologies used to generate information to explore this question. Details for the complete study can be found in Chapter 6.

2.5.1. Data Collection Process

This chapter collected and assessed the relevant literature using the scoping review method developed by Arksey and O'Malley (29). A list of search terms was used in the five data sources (details of search terms and search strategy are available in Chapter 6). Two reviewers were involved and data collection steps involved removal of duplicate literature material, and applying the inclusion and exclusion criteria (listed in Chapter 6). Both reviewers independently applied the inclusion/exclusion criteria in the review process. From each selected relevant article, general topics were extracted and documented. Further details available in Chapter 6.

2.5.2. Study Design

We conducted a scoping review, as described by Arksey and O'Malley, to identify factors and corresponding themes that affect the treatment decision-making of localized PCa patients in Canada and the United States (29). The themes within the relevant literature were identified using principal component analysis (30-32). In addition, a Word Cloud consisting of information from the title and abstracts of the relevant literature was generated to assess

complementary results to the principal component analysis. The use of a scoping review, principal component analysis, and a word cloud provided a systematic process for identifying overarching themes in the literature regarding factors affecting PCa treatment decision-making.

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CHAPTER 3 – GEOGRAPHIC DISPARITIES IN PROSTATE CANCER AND ITS ASSOCIATION WITH PHYSICIAN DENSITY IN SASKATCHEWAN: ANALYSIS USING BAYESIAN MODELS

Article reproduced with permission and minor edits. Originally published as: Andkhoie M, Szafron M. Geographic disparities in prostate cancer and its association with physician density in Saskatchewan: analysis using Bayesian models. *BMC Cancer*. 2021. 21(1): 948; https://dx.doi.org/10.1186/s12885-021-08646-2. My contributions to this study include data acquisition, study design, data analysis, interpretation of findings and manuscript preparation.

In this chapter, we present the complete study used to address the research question *"*Is the PCa incidence in Saskatchewan affected by changes in family physician density, the remoteness level of where a patient lives, and the closest PCa assessment centre from where a patient lives?" associated with our first study objective "to determine the associations (if any) between components of healthcare access and each of PCa incidence, treatment usage and time-to-treatment trends among Saskatchewan patients". Specifically, in this chapter, we identify clusters of higher and lower than expected prostate cancer (PCa) incidence in Saskatchewan. Further, we assess the effects of family physician density on the estimated PCa incidence in Saskatchewan. We identify clusters of PCa stratified by risk levels using Global Moran's I, Local Moran's I and Kuldorff's Spatial Scan Statistics. We then estimate the standardized incidence ratios (SIRs) of PCa and their association with family physician density in Saskatchewan using the Besag, York and Mollie (BYM) Bayesian method. Clustering analysis identified higher than expected clusters of crude SIR for metastatic PCa in north-east Saskatchewan and lower than expected clusters in south-east Saskatchewan. Areas in north-west Saskatchewan have lower than expected crude SIR for both intermediate-risk and low-risk PCa. Family physician density was negatively associated with SIR of metastatic PCa (IRR: 0.935 [CrI: 0.880 to 0.998]) and SIR of high-risk PCa (IRR: 0.927 [CrI: 0.880 to 0.975]). We identify the geographical disparities in risk-stratified PCa incidence in Saskatchewan. Finally, we show that areas with lower densities of family physicians have higher than expected incidences of metastatic and high-risk PCa. Hence policies to increase physician supply should ensure an equitable geographic distribution of primary care physicians to support early detection of diseases, including PCa.

3.1. Introduction

Prostate cancer (PCa) accounts for about 20% of all new cancer cases among men in Canada (1). Within Canada, the incidence rate of PCa varies between provinces. In 2019, Saskatchewan had the third highest projected age-standardized PCa incidence rate (117.8 cases per 100,000 in 2019) when compared to other Canadian provinces (1). In addition, the Saskatchewan age-standardized PCa incidence rates have remained higher than the national Canadian rates for the majority of the past 10 years (1, 2). Previous studies have shown geographic factors influence PCa outcomes in Saskatchewan (3, 4), hence this study explores the influence of geographic patterns on PCa incidence rates in Saskatchewan.

Saskatchewan, in terms of geography, has the second lowest population density in Canada (after Newfoundland), with a majority of the province being sparsely populated and nearly 40% of the Saskatchewan population living in rural areas (5). Because cancer patient outcomes are worse for rural dwellers compared to urban dwellers (6-10) and Saskatchewan has a relatively large rural population (5), it is possible that the rates for different PCa risk levels are associated with the geographic distribution of Saskatchewan residents.

The low population density of Saskatchewan results in the geographic factors of remoteness and commute time being healthcare access barriers for Saskatchewan residents (3, 4, 11, 12). The low population density also impacts the distribution of physicians in the province. Saskatchewan has one of the lowest per capita physician supplies (also known as physician density) compared to the other provinces in Canada (190.3 per 100,000 in 2014 and 204.5 per 100,000 in 2018) (13). Because one mechanism for improving health outcomes, including reductions in PCa-specific mortalities, is increasing physician supply (14-20), understanding the associations (if any) between physician density and PCa risk level incidence is crucial to improving PCa outcomes in Saskatchewan.

While the factors leading to such high Saskatchewan PCa incidence rates are unknown, we hypothesize that the unique geography of Saskatchewan may be contributing to the high incidence of PCa in Saskatchewan. In this study we explore the geographic distribution of PCa cases in Saskatchewan. In addition, since the incidence for advanced cancers is known to decrease with the increase in availability of physicians (18, 21, 22), we identify the association

(if any) that exists between the family physician density and PCa standardized incidence ratios (SIRs) in Saskatchewan.

The first study objective is to estimate the PCa SIRs in Saskatchewan stratified by PCa risk levels. The second objective is to identify clusters of higher than and lower than expected PCa SIRs in Saskatchewan stratified by PCa risk level. The final objective is to identify any associations between family physician density and the estimated PCa SIRs in Saskatchewan.

3.2. Methods

3.2.1. Data and Study Area

The data for PCa were from the Saskatchewan Cancer Registry (SCR) and consisted of demographic, clinical, and geographic information for 3,526 patients diagnosed with PCa between 2010 and 2014. Based on the demographic information, all PCa patients were age 35 years or over. The study area contained 82 geographic areas (GAs) in central and southern Saskatchewan categorized (for privacy reasons) by the SCR using residence codes (Figures 3.1 and 3.2) (23). From 2010 to 2014, the study area contained 3,289 PCa patients, after excluding those living out-of-province at the time of diagnosis (194 patients) and those (43 patients) living in the three northern regions (Mamawetan Churchill River, Keewatin Yatthe, and Athabasca). The northern regions were excluded because these regions could not be subdivided due to privacy reasons. Of these 3,289 PCa patients, the analysis further excluded 298 patients because their PCa risk levels were unknown. Therefore, the final sample had 2,991 patients, each categorized per the GA in which the patient lived at the time of diagnosis.

To calculate the SIRs (described in the following sections), population counts for 2012 from the Saskatchewan Covered Population (SCP) were used in the denominator in the formula for calculating a PCa SIR (see Definitions section) (23). The SCP is a count of residents with provincial health insurance in Saskatchewan in a given year and is maintained by Government of Saskatchewan (23). Because all PCa patients in the SCR dataset were age 35 or over, the SCP data used were for men over the age of 35. The overall SCP for men age 35 or over deviated less than 3% each year (24), therefore we chose to use statistics from the midpoint year 2012 (between 2010 and 2014) for the denominators in the calculations (25).

To calculate physician density (described in the following sections) for the period 2010 to 2014, the required data from the Canadian Medical Association were only available for 2011 (26). Hence our estimated physician densities are based on the year 2011. Canadian Medical Association data consist of family physicians and general practitioners licensed to practice medicine in Saskatchewan.

The relative variability of PCa incidence between the time period (2010 to 2014) was assessed using the coefficient of variation (ratio of the standard deviation to the average).

The University of Saskatchewan BioMedical Research Ethics Board provided ethics approval (Bio-REB certificate #15-34).

3.2.2. Definitions

The risk levels (low, intermediate, high) for PCa were based on the Genitourinary Radiation Oncologists of Canada (GUROC) definitions (27) and a fourth risk level ("metastatic") was added to include patients diagnosed with metastatic cancer. For each risk level, the expected number of PCa cases in the i^{th} GA (E_i) was calculated as follows (28):

$$E_i = n_i \left(\frac{\sum_i O_i}{\sum_i n_i}\right), \tag{3.1}$$

where n_i and O_i respectively denote the population count of men age 35 or over and the observed number of PCa cases in the i^{th} GA. For each PCa risk level, the standardized incidence ratio (SIR) (which will be referred to as the crude estimated SIR) was estimated by dividing the number of observed cases in each GA by the number of expected cases in each GA (28).

3.2.3. Independent Variables

The study variables of interest were physician density, GA remoteness index, and closest PCa assessment centre to a GA. For each GA, the family physician density was calculated using the 2011 Canadian Medical Association data, with the same population denominator used for the expected count of PCa cases. A remoteness index for a GA was calculated using the average of the Statistics Canada remoteness indices for regions forming the GA [29]. For each GA, the closest PCa assessment centre was categorized as Regina or Saskatoon, based on the shortest Euclidean distance between the centroid of the GA and the centroids of Saskatoon and Regina.

Further details regarding GA remoteness index and closest PCa assessment centre variables used in this study can be found in the literature (3, 4).

3.2.4. Statistical Methods

Clustering analysis was conducted to identify spatial clusters of PCa SIRs by each risk level. Second, for each PCa risk level, a null model was built where the crude estimated SIRs were smoothed spatially using the method proposed by Besag, York and Mollie (BYM model) (29). The estimated SIRs from the BYM models will be referred to as the smoothed estimated SIRs. Third, ecological analyses were conducted to assess any associations between the independent variables and the smoothed estimated SIRs for each of four PCa risk levels.

3.2.5. Clustering Analysis

For each risk level, Global Moran's I was calculated using the crude estimated SIR value for each GA (30). The statistical significance for Global Moran's I statistic was calculated using 999 permutations (30), which, if significant, demonstrates that the GAs sharing common boundaries have similar SIRs instead of having random geographically-distributed SIRs (31). GAs within a 120-km radius of a GA were identified as neighbours of the GA. The corresponding weight matrix for the analysis was then computed using the inverse of the Euclidean distances between the centroids of a GA and its neighbours. This weight matrix was chosen to reflect the suspected correlation structure of the data (32).

For each risk level with statistically significant Global Moran's I values, the crude estimated SIRs were studied further using the Local Moran's I and Kuldorff's Spatial Scan statistics (33-35).

3.2.6. BYM Modeling

The SIRs were estimated using a Bayesian model-based approach to ensure, if spatial correlation exists, the estimated SIRs (i.e., the smoothed estimated SIRs) were corrected for any spatial dependence between the GAs.

First, for each PCa risk level, a null model was built where the smoothed estimated SIRs were computed using the Bayesian BYM method (29). Due to the count nature of the data, we assume our observed data O_i follows a Poisson distribution (36) with mean $E_i\theta_i$ where E_i and θ_i

respectively denote the expected number of PCa cases and the "true" SIR in the i^{th} GA (37, 38). The BYM method models the log of the SIR as follows:

$$\text{Log}(\theta_i) = c + u_i + v_i, \quad (3.2)$$

where intercept c is the mean, and the terms u_i and v_i respectively denote the spatially structured and unstructured random effects (37, 38).

The parameters used in this model are based on the literature (37-41). The random effects and the intercept are assigned prior distributions. The intercept was assigned a uniform prior that extends over the whole real line (37, 38). The spatially structured random effect u_i was assumed to follow a conditional auto-regressive distribution and the unstructured random effect v_i was assumed to follow a normal distribution with mean zero (37, 38). The variability for both random effects were controlled by a precision parameter. The precision parameter for the random effects were assigned a Gamma distribution with hyper-prior specification of (0.5, 0.0005) (39, 41).

The simulation for each model consisted of three chains (42, 43). Each chain consisted of 200,000,000 iterations to obtain 50,000 data points: one taken every 4000 iterations. A burn-in period of 8,000,000 iterations was selected based on the characteristics of the Brooks-Gelman-Rubin plots (38, 42, 43). To determine whether the generated estimates for each parameter were from the correct distribution, the following were used: potential scale reduction factor, (42) stationarity and half-width tests, (44) Z-score for equality of the means, (45) and run length control (46, 47)).

3.2.7. Ecological Analysis

Using the BYM models, unconditional analyses were conducted to identify any associations between the independent variables and the SIRs for each risk level. The statistical significance of an independent variable was determined via its 95% credible interval (CrI).

Global and Local Moran's I statistics were computed using Geoda 1.12 (48). Kuldorff's Spatial Scan Statistic was computed using SatScan™ v9.4 (49). SIR maps were built using quantum Geographical Analysis System (QGIS.org) Version 3.12 (50). BYM models were built in OpenBUGS version 3.2.3 (51). Convergence diagnostics for the BYM models were conducted in R using the package 'coda' (52).

3.3. Results

The study sample consisted of an average count of 598 PCa cases per year between 2010 and 2014, and the coefficient of variation for PCa incidence between 2010 and 2014 was 7.9%. During the five-year period, the coefficient of variation for remoteness index and physician density were 1.4% and 5.0%, respectively. Based on the age demographic information of all cases, a majority of the PCa cases were 70 years or older, followed by those who were 60 to 69 years old (Table 3.1). However, the distribution of the age demographics varied by risk level. Low and intermediate risk PCa cases had higher proportions of cases in the younger age groups. In contrast, high risk and metastatic cases had higher proportions of cases in the older age groups. Among all cases, each year (between 2010 and 2014) the proportion of cases diagnosed was about 20% with deviations of less than 2%. See Table 3.1 for details.

Table 3.1. Descriptive statistics of the prostate cancer cases stratified by GUROC risk levels (n=2991).

Count (proportion)	Metastatic	High Risk	Intermediate	Low Risk	Total
Age					
< 60 years	27 (6.7)	168 (15.4)	277 (26.2)	118 (26.6)	590 (19.7)
60 to 69 years	87 (21.6)	393 (36.1)	458 (43.4)	224 (50.5)	1162 (38.9)
70 years or older	288 (71.6)	528 (48.5)	321 (30.4)	102 (23.0)	1239 (41.4)
Year of diagnosis					
2010	81 (20.2)	193 (17.7)	206 (19.5)	84 (18.9)	564 (18.9)
2011	73 (18.2)	252 (23.1)	211 (19.8)	104 (23.4)	640 (21.4)
2012	58 (14.4)	223 (20.5)	265 (25.1)	113 (25.5)	659 (22.0)
2013	89 (22.1)	213 (19.6)	197 (18.7)	66 (14.9)	565 (18.9)
2014	101 (25.1)	208 (19.1)	177 (16.8)	77 (17.3)	563 (18.8)
Total	402 (100.0)	1089 (100.0)	1056 (100.0)	444 (100.0)	2991 (100.0)

The highest proportion of cases were high-risk PCa (36.4%) followed by intermediate-risk (35.3%), low-risk (14.8%) and metastatic cases (13.4%). In nearly a third of GAs (32.9%), the observed incidence of metastatic PCa was more than 50% than the expected incidence. In 28%, 18% and 24% of GAs, the observed incidences of high-risk, intermediate-risk and low-risk PCa, respectively, were more than 50% than the expected incidence. See Table 3.2 for details.

Table 3.2. Descriptive statistics of prostate cancer cases diagnosed within each geographic area (82 areas).

	Metastatic	High Risk	Intermediate	Low Risk
Crude estimated SIR				
>50% less than expected	21 areas	9 areas	16 areas	24 areas
10% to 50% less than expected	15 areas	25 areas	23 areas	17 areas
Within 10% expected	10 areas	12 areas	9 areas	6 areas
10% to 50% more than expected	9 areas	13 areas	19 areas	15 areas
50% to 100% more than expected	15 areas	13 areas	7 areas	8 areas
>100% more than expected	12 areas	10 areas	8 areas	12 areas

3.3.1. Clustering Analysis

The pattern of crude estimated SIRs for each PCa risk level in Saskatchewan is visualized in Figure 3.1. Spatial patterns within Figure 3.1 are identified using clustering analysis. The Global Moran's I statistics for the crude estimated SIRs for each PCa risk level (except for high-risk) show evidence of positive spatial autocorrelation (Table 3.3). Hence, there was evidence that some geographical areas in Saskatchewan sharing boundaries have similar crude estimated SIRs for metastatic, intermediate and low risk PCa, instead of a random distribution of incidence patterns.

Table 3.3. Result of the Global and Local Moran's I analysis stratified by GUROC risk levels.

	Metastatic	High Risk	Intermediate Risk	Low Risk
Global Moran's I statistic	0.132*	0.058	0.128*	0.106*
Local Moran's I				
High-High	4 areas	-	8 areas	2 areas
Low-Low	9 areas	-	13 areas	15 areas
Low-High	4 areas	-	0 areas	4 areas
High-Low	4 areas	-	2 areas	1 area
Not Significant	61 areas	-	59 areas	60 areas

*statistically significant at 5% level of significance

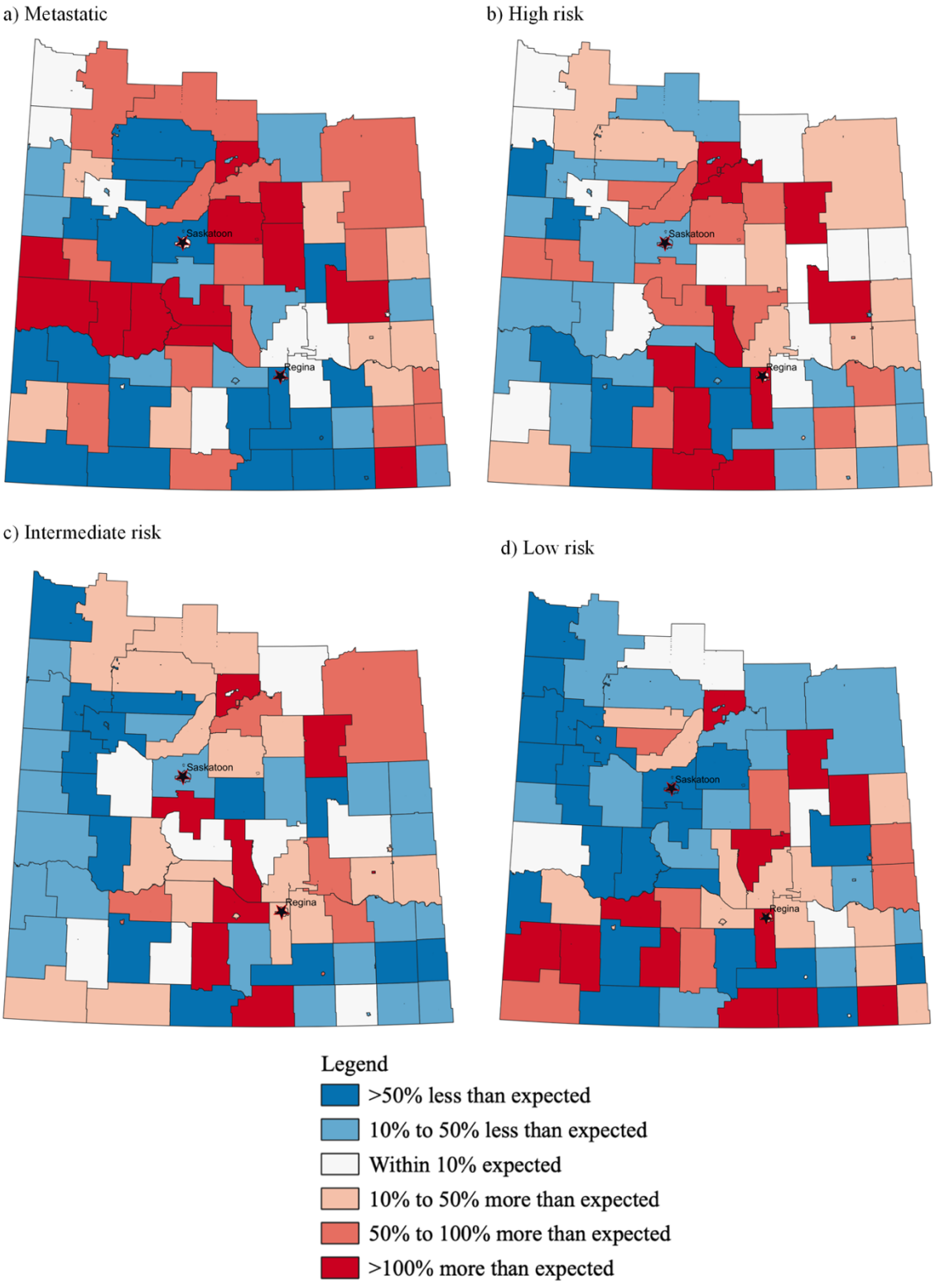

Figure 3.1. Crude estimated standardized incidence ratios (SIRs) for metastatic, high-risk, intermediate-risk, and low-risk prostate cancer cases in Saskatchewan (2010 to 2014).

Using the Local Moran's I statistic, clusters of crude estimated SIRs for each PCa risk level were identified. In Figure 3.2, "high-high" clusters of metastatic PCa are identified in the north-east part of the study area. Hence, areas in north-east Saskatchewan have higher-than-average crude estimated SIRs for metastatic PCa. For intermediate-risk and low-risk PCa, "low-low" clusters are identified in the north-west part of the study area. Therefore, areas in north-west Saskatchewan have lower-than-average crude estimated SIRs for both intermediate-risk and low-risk PCa (Figure 3.3 and Figure 3.4).

For Kuldorff's Spatial Scan Statistic, the maximum spatial window size for metastatic, intermediate and low risk PCa were equal to or less than 30%, 25% and 25%, respectively, of the total population. Kuldorff's Spatial Scan Statistic identified a higher-than-the-average cluster of crude estimated SIRs for metastatic PCa in north-east Saskatchewan and lower-than-the-average cluster in south-east Saskatchewan, analogous to the clusters identified using the Local Moran's I statistics (Figure 3.2). Similarly, the spatial scan statistic results for intermediate-risk and low-risk PCa were comparable to the clusters identified using the Local Moran's I statistics described earlier (Figure 3.3 and Figure 3.4).

3.3.2. BYM Modeling

The crude and smoothed estimated SIRs for a GA are illustrated in Figure 3.5. For both metastatic and high-risk PCa, the smoothed BYM estimates highlight areas of elevated incidence in north-east part of Saskatchewan (Figure 3.5). Also in Figure 3.5, the smoothed estimated SIRs for intermediate-risk and low-risk PCa identify areas of low incidence in north-west part of Saskatchewan. Table 3.4 illustrates how the crude estimated minimum and maximum SIR values are adjusted by the BYM modelling.

Table 3.4. Comparison of minimum and maximum values of smooth estimated standardized incidence ratios (SIRs) and crude estimated SIRs stratified by GUROC risk levels.

	Crude estimated SIRs		Smoothed estimated SIRs	
Outcome	Min	Max	Min	Max
Metastatic	0.000	3.474	0.921	1.221
High Risk	0.213	3.633	0.883	1.218
Intermediate Risk	0.000	5.888	0.347	3.093
Low Risk	0.000	4.470	0.235	2.348

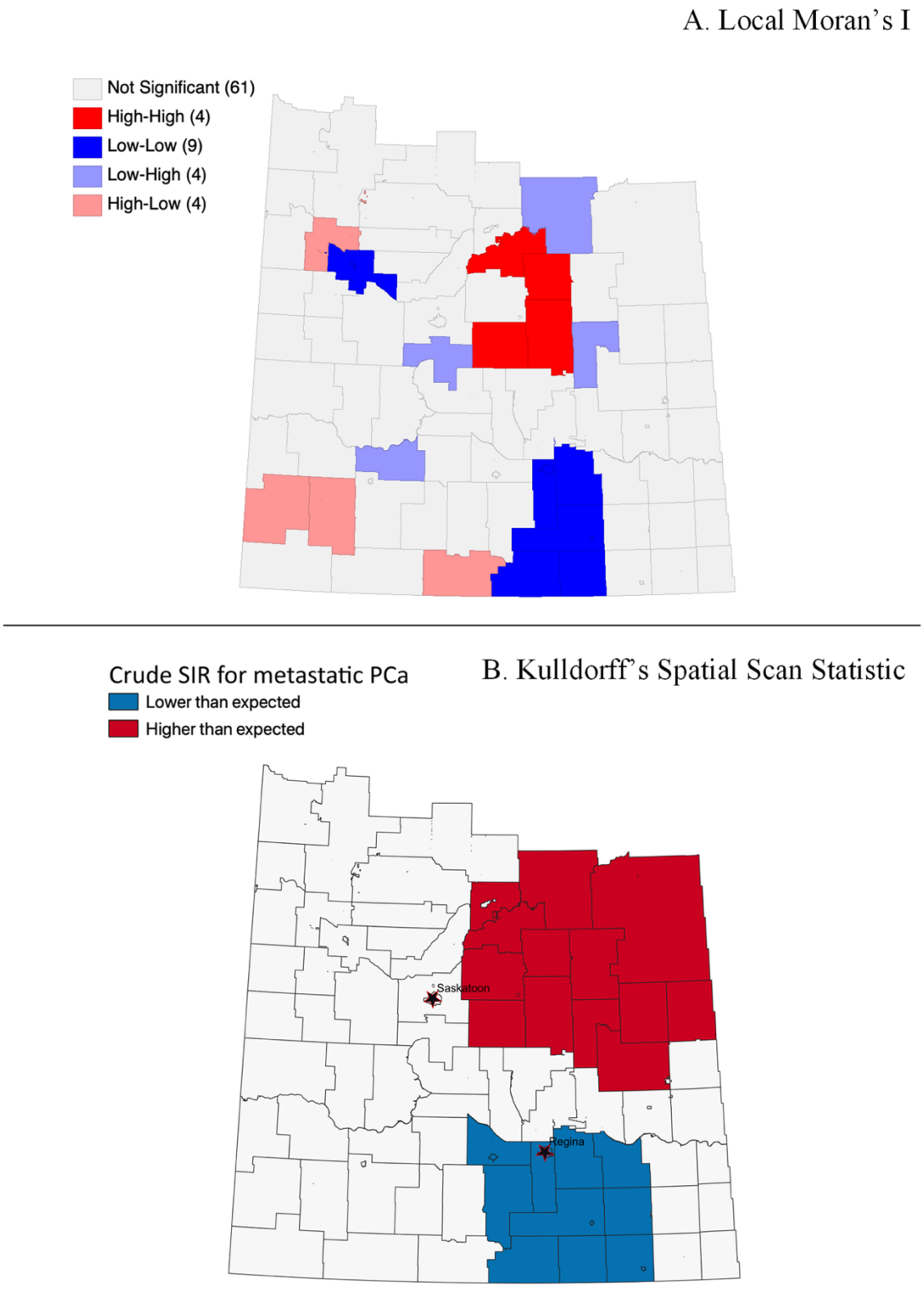

Figure 3.2. Metastatic prostate cancer crude estimated SIRs clustering analysis: (A) Local Moran's I; (B) Kuldorff's Spatial Scan Statistic.

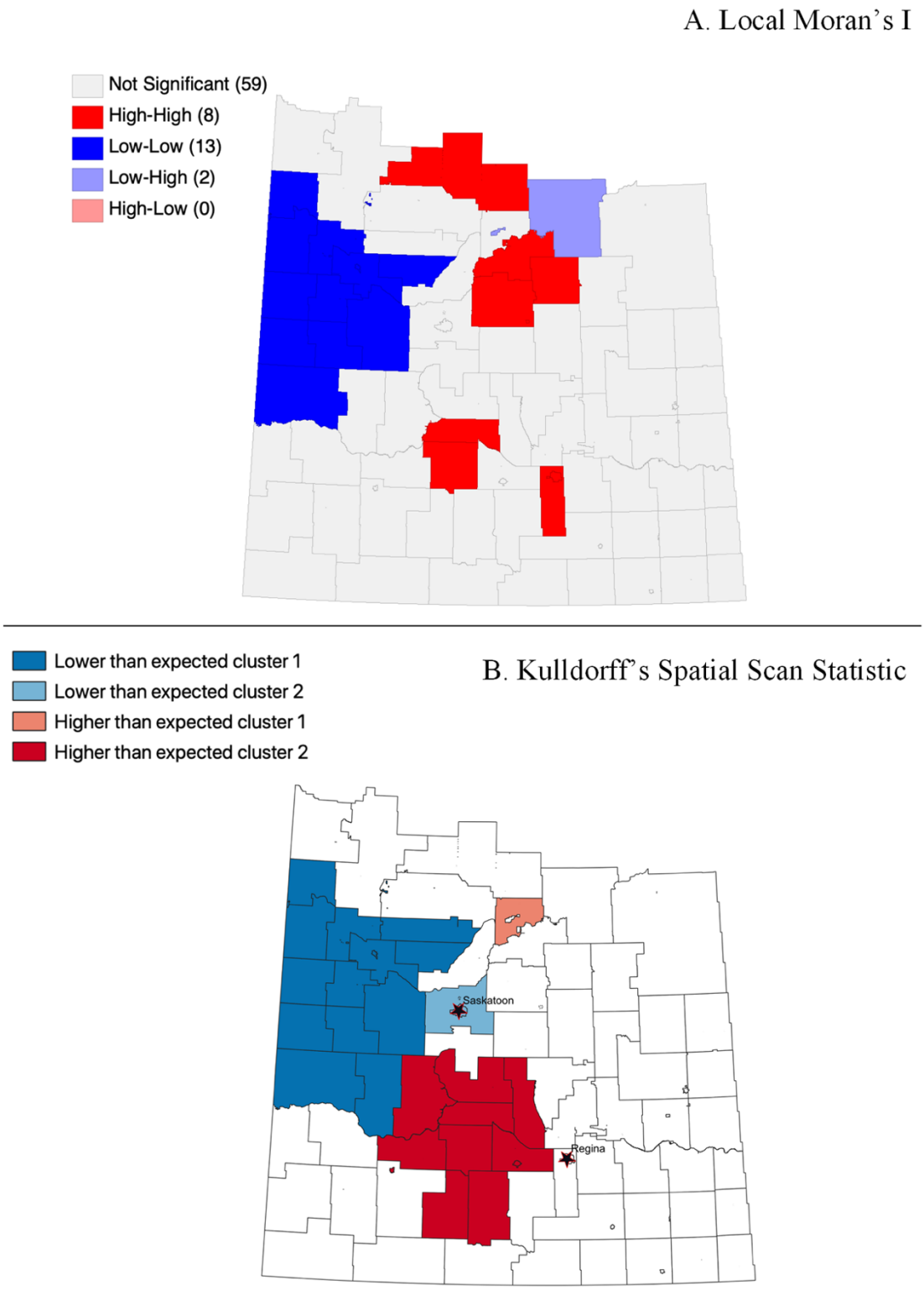

Figure 3.3. Intermediate-risk prostate cancer crude estimated SIRs clustering analysis: (A) Local Moran's I; (B) Kuldorff's Spatial Scan Statistic.

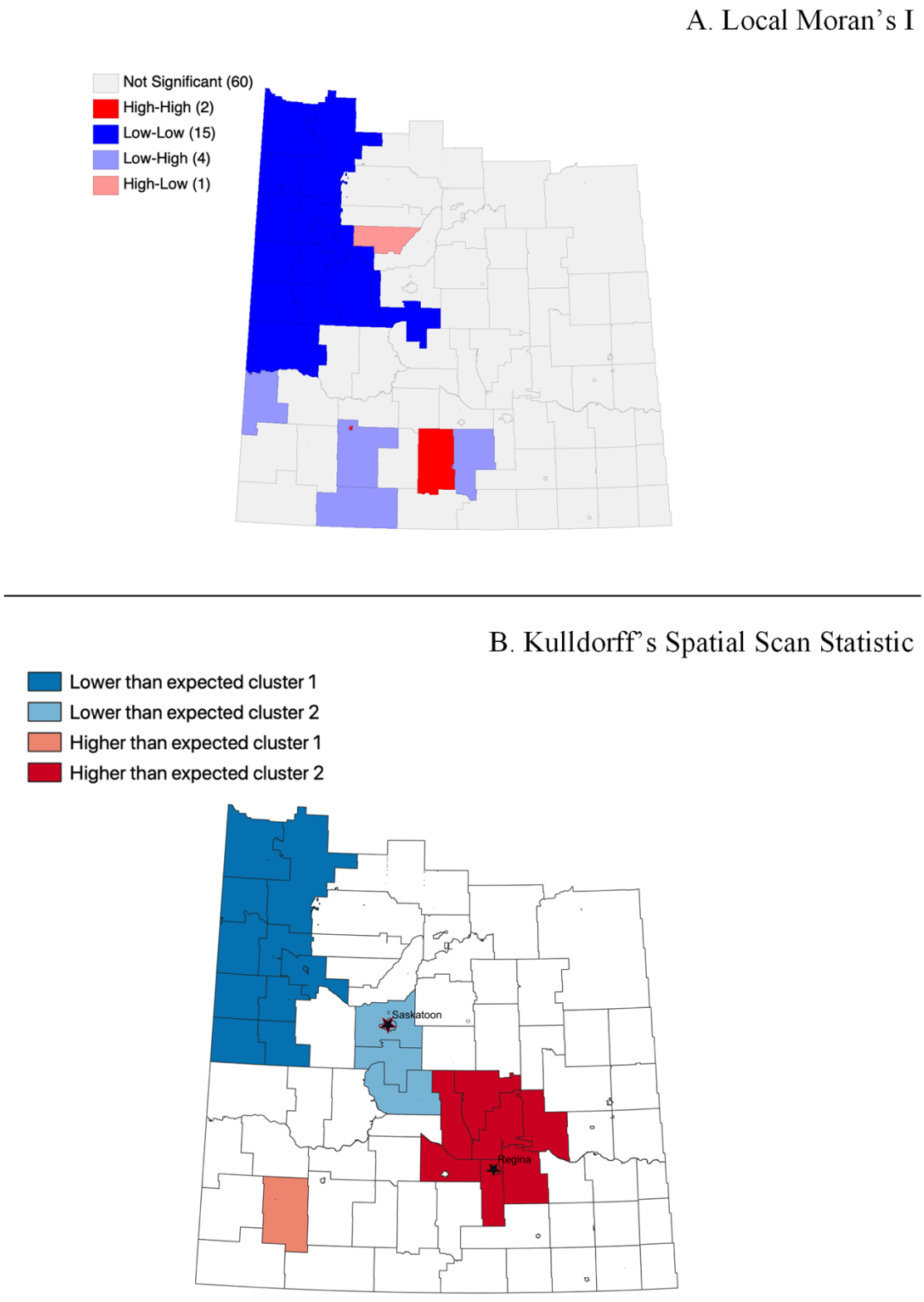

Figure 3.4. Low-risk prostate cancer crude estimated SIRs clustering analysis: (A) Local Moran's I; (B) Kuldorff's Spatial Scan Statistic.

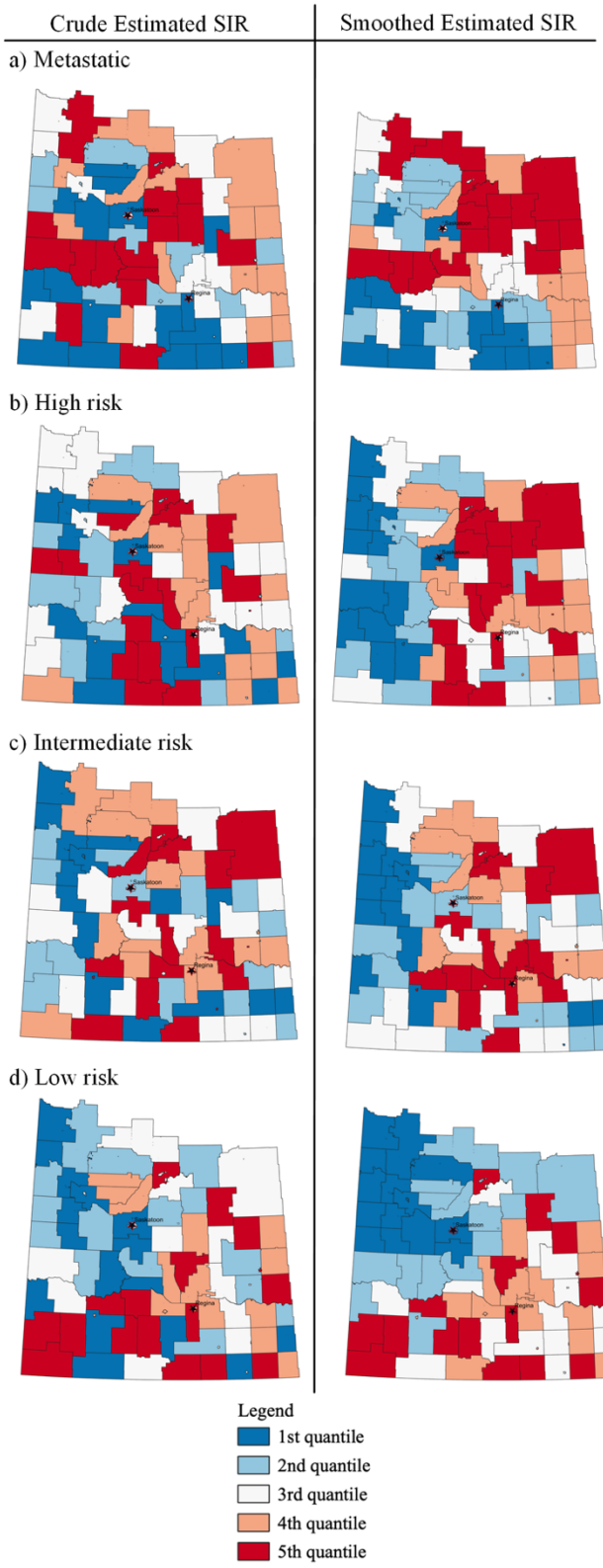

Figure 3.5. Quantile distribution of prostate cancer crude estimated SIRs (left) and smoothed estimated SIRs (right) by GUROC risk levels.

3.3.3. Ecological Analysis

Family physician density was negatively associated with the smoothed estimated SIRs for metastatic PCa (IRR: 0.935 [CrI: 0.880 to 0.998]) and for high-risk PCa (IRR: 0.927 [CrI: 0.880 to 0.975]). Based on the mean coefficient of family physician density for metastatic PCa (Table 3.5), one unit increase (or increase of 1 physician per 1,000 population) would be equal to an average decrease in metastatic PCa SIR by 6.5%. Similarly, an average increase of 1 physician per 1,000 population would be equal to an average decrease in high-risk SIR by 7.3%. Figure 3.6 provides geographic pattern of family physician density in Saskatchewan and comparison with Figure 3.5 visually complements the negative correlation with metastatic PCa and high-risk PCa. For intermediate-risk and low-risk PCa, based on the credible intervals, there was no evidence of association with family physician density (Table 3.5).

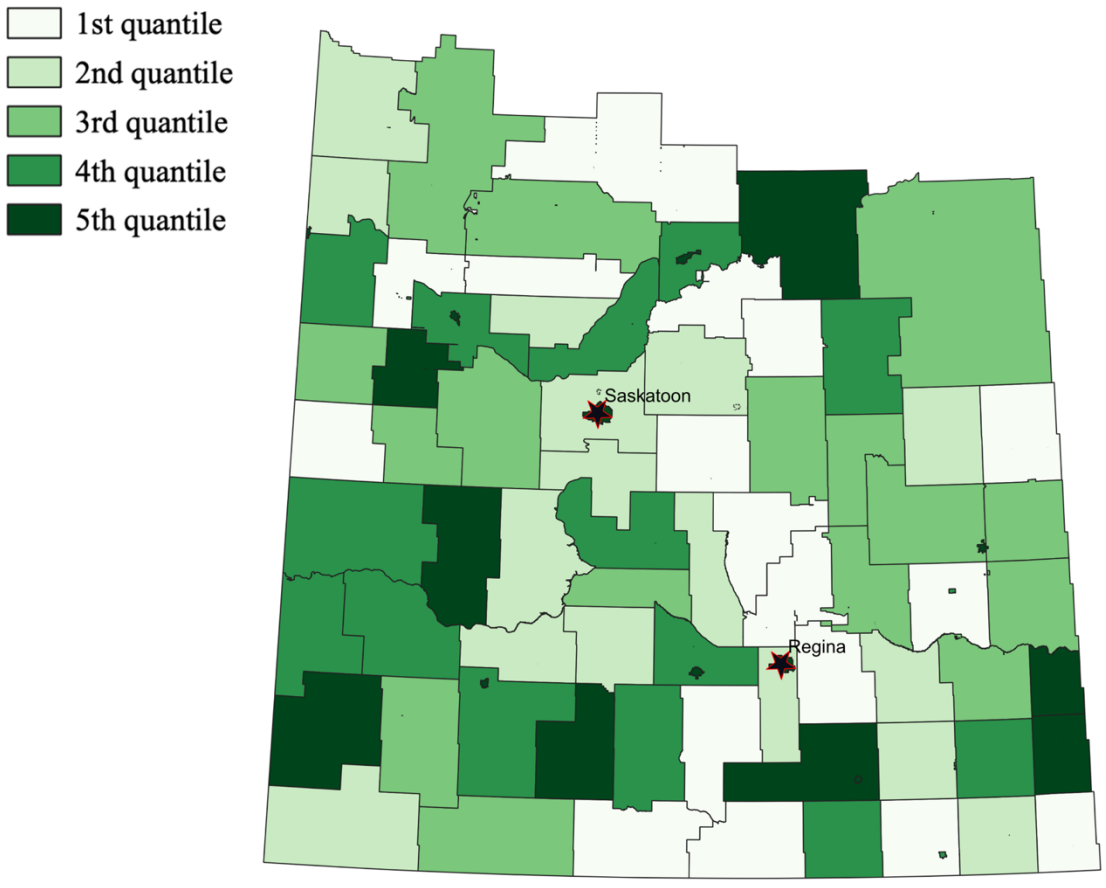

Figure 3.6. Quantile distribution of family physician density in Saskatchewan (2011).

Table 3.5. Result of the Bayesian analysis proposed by Besag, York and Mollie (BYM method).
Physician Density (Number of physicians per 1,000 population)

Outcome	Mean	Credible Interval	Incidence Rate Ratio (Credible Interval)
Metastatic	-0.067	-0.128 to -0.002	0.935 (0.880 to 0.998)
High Risk	-0.076	-0.128 to -0.025	0.927 (0.880 to 0.975)
Intermediate Risk	-0.041	-0.109 to 0.026	Not significant
Low Risk	-0.009	-0.079 to 0.062	Not significant

There was no evidence of any association between the SIR of each PCa risk levels and the two remaining independent variables (closest PCa assessment centre to a GA and GA remoteness index).

3.4. Discussion

This study estimated risk stratified PCa SIRs in Saskatchewan to identify if any geographic patterns and disparities. The geographic patterns of the risk stratified SIRs identified areas of concern (higher than expected SIRs) in Saskatchewan using Bayesian models and traditional clustering analysis methods. This study found clustering of higher than expected incidence for metastatic PCa in north-east part of Saskatchewan, and lower than expected incidence in south-east part of Saskatchewan. This study also identified lower than expected incidence of intermediate-risk and low-risk PCa in the north-west part of Saskatchewan. The estimation of SIRs using the BYM method led to adjustment of the crude estimated SIRs to facilitate identification of spatial trends (53).

Our study also shows that areas with lower density of family physician have higher than expected incidence of metastatic and high-risk PCa. A similar trend has been observed in the United States where increases in primary care physician density were associated with a decrease in late-stage diagnosis of cancers including PCa (21, 54). The findings of this study highlight the effect that increasing physician supply may have on improving health outcomes, as identified in previous studies including PCa (14-20). The results also highlight the wide-ranging distribution of family physicians within Saskatchewan, acknowledging Saskatchewan also has one of the

lowest per capita physician supplies compared to the other provinces in Canada (13). Hence, policies to increase physician supply should ensure equitable geographic distribution of primary care physicians to support early detection of diseases including PCa.

Nearly half of the patients in the sample were high risk (36.4%) or metastatic (13.4%), which could be indicative of physician practice variations including receptiveness towards PCa screening policies. Literature shows that physician beliefs regarding PCa screening/diagnosis procedures can influence their practice (physicians who are uncertain about PCa screening/diagnosis procedures are less receptive towards offering PCa screening/diagnosis to their patients) (55). Because such practice variations possibly exist among Saskatchewan physicians suggested by the historical PCa screening trends (56, 57) and the literature reports that an increase in advanced PCa may be due to a decrease in PCa screening (58), physician beliefs might possibly explain the geographic variations in PCa diagnosis rates.

Although family physician density was not associated with diagnostic pattern for low-risk and intermediate-risk PCa, further research is needed if these regional trends are related to physician practices given the controversy of screening tests for early detection of PCa (59, 60). Given recent research showing PCa screening and detection of early-stage PCa decreasing, potentially due to mixed PCa screening guidelines, further studies assessing the role of PCa screening guidelines on geographic disparities in early-stage PCa incidence may provide further explanation (61).

This study identifies the geographical disparities in risk-stratified PCa incidence in Saskatchewan. This study suggests that healthcare access factors (62), including availability of physicians and the geographic location of individuals, may affect health outcomes for PCa. This study further highlights the possibility that enhancing health delivery in rural areas may improve health outcomes. A recent report by the Rural Road Map Implementation Committee in Canada shows there are continued challenges regarding healthcare access in rural parts of Canada, including difficulties of attracting and retaining physicians (63).

The limitations of this study include the use of aggregate data for the ecological study design due to lack of information on individual-level data on family physician availability to the

patient. However, the study uses widely developed Bayesian and conventional spatial analysis methods to identify inherent patterns in the study area.

3.5. Conclusions

This study identified geographic disparities in PCa incidence in Saskatchewan. There were higher than expected incidence of metastatic PCa in north-east parts of Saskatchewan, and lower than expected incidence of intermediate-risk and low-risk PCa in the north-west part of Saskatchewan. In addition, areas with lower density of family physician had higher than expected incidence of metastatic and high-risk PCa. This study shows that availability of community level healthcare providers and geographic location of patients affects cancer care in Saskatchewan. This highlights the need for adequate availability of primary care physicians in rural and urban areas to improve cancer care in Saskatchewan.

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CHAPTER 4 – THE IMPACT OF GEOGRAPHIC LOCATION ON SASKATCHEWAN PROSTATE CANCER PATIENT TREATMENT CHOICES: A MULTILEVEL AND SPATIAL ANALYSIS

Article reproduced with permission and minor edits. Originally published as: Andkhoie M, Szafron M. The impact of graphic location on Saskatchewan prostate cancer patient treatment choices: a multilevel and spatial analysis. *J Rural Health*. 2020; 36(4): 564-576; https://dx.doi.org/10.1111/jrh.12471. My contributions to this study include data acquisition, study design, data analysis, interpretation of findings and manuscript preparation.

In this chapter, we present the complete study used to address the research question "Are the PCa treatment utilization rates in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?" associated with our first study objective "to determine the associations (if any) between components of healthcare access and each of PCa incidence, treatment usage and time-to-treatment trends among Saskatchewan patients". Specifically, in this chapter we estimate the relationship between remoteness and the initial chosen treatment: active surveillance/watchful waiting (AS/WW), radiation therapy (RT), surgery, chemotherapy (CT), or hormonal therapy (HT) for prostate cancer (PCa). We built 2 multilevel generalized linear models via a binomial link for each treatment type (one with only covariates and one with 2 study variables added to the covariate model). In addition, we also used cluster analysis using the Global and Local Moran's I spatial statistics to find any complementary results to the above models. We found that patients living in the rural areas have lower odds (OR = 0.59; 95% CI, 0.45-0.77; $P < 0.001$) of having surgery compared to patients living in the greater urban areas. Among patients whose closest PCa assessment centre is Regina, patients living in the greater urban areas have higher odds (OR = 1.66; 95% CI, 1.03-2.68; $P = 0.039$) of choosing RT compared to patients living in the rural areas. There was no statistically significant effect of remoteness on whether one chose HT or AS/WW. There are regional disparities in PCa treatment utilization. Living in rural areas affects choosing surgery and, in certain localized geographical regions, affects choosing RT. For non-curative treatments (i.e., AS/WW and HT), we did not find any association with geographical remoteness.

4.1. Introduction

In Canada, prostate cancer (PCa) is the second leading cause of cancer among men (after lung cancer) with approximately 1 in 8 males diagnosed in their lifetime (1). While the Canadian 5-year relative PCa survival rate is 96%, the rates vary among the provinces, with Saskatchewan ranking second lowest (91%) (1). According to a 2015 national report, Saskatchewan also had the second highest (26 deaths per 100,000) age-standardized PCa mortality rate (1). While each Canadian province individually administers PCa treatments and approved treatments are available at no charge through Canada's universal health care system, it is unknown why Saskatchewan has these poor PCa outcomes (when compared to other provinces) (2).

In Canada, rural and remote areas are known to face access barriers to health care services, including the availability of health care providers and long travel distances to health care facilities (3-6). In addition, transportation issues further add barriers to patients' treatment decisions in rural regions (7). Multiple studies have shown that patients living in rural regions may compromise their cancer treatment decision, notably due to longer travel time and distance to access treatment centres (8-14). Because Saskatchewan has a relatively large rural population, Saskatchewan PCa patients living in rural geographic locations may face these issues regarding accessibility to health care services including cancer treatments (3-6, 15). Hence PCa patients might choose their PCa treatments based on where they reside rather than the optimal treatments available for their PCa pathology.

In this work we explore the relationship between where Saskatchewan PCa patients reside and their treatment utilization, where the treatment choices include active surveillance/watchful waiting (AS/WW), surgery, radiation therapy (RT), chemotherapy (CT), and hormonal therapy (HT) (16). Studies show that rural patients have lower utilization for cancer treatments including for breast and lung cancers, but not consistently for PCa treatments (8, 11, 13, 17, 18). It is not known whether any relationship exists between geographic remoteness and PCa treatment utilization in Saskatchewan. We hypothesized that those living in rural areas would have higher non-curative treatment utilization (i.e., AS/WW and HT), and those living in urban areas would have higher curative treatment utilization (i.e., RT, CT, and surgery).

4.2. Methods

4.2.1. Data

Data for PCa patients diagnosed during 2010 through 2014 were sourced from the Saskatchewan Cancer Registry, a database of cancer health information (including treatment-related information) for cancer patients diagnosed in Saskatchewan. While the Registry contained information for 3,526 PCa patients diagnosed during the study period, the final sample used consisted of 3,289 patients (93.3%), after excluding patients living out-of-province at the time of diagnosis (194 cases) and those (43 cases) living in the 3 former northern health authorities (Mamawetan Churchill River, Keewatin Yatthe, and Athabasca). Those living in the northern health authorities were excluded because for privacy reasons these health authorities could not be subdivided into smaller geographic areas (GAs). The University of Saskatchewan BioMedical Research Ethics Board provided ethics approval (Bio-REB certificate #15-34).

4.2.2. Variables

For each of the treatments—surgery, RT, HT, or CT—we derived a corresponding variable coded as "Yes" if, after PCa diagnosis, a patient received the treatment within 2 years after their diagnosis date, or "No" otherwise. For AS/WW, we derived a variable coded as "Yes" if a patient did not undergo any of these 4 treatments within 2 years after PCa diagnosis, or "No" otherwise. The "within 2 years" treatment definition is adapted from the radiation therapy utilization definition developed by Canadian Partnership Against Cancer (19). Patients may get multiple treatments within 2 years of diagnosis; therefore, surgery, HT, CT, or RT are not mutually exclusive. For HT, only drug-based treatments were captured (i.e., this excludes orchiectomy).

For privacy reasons, the Saskatchewan Cancer Registry subdivided central and southern Saskatchewan into 82 GAs using residence code boundaries (see Figure 4.1) (20). The Census Metropolitan Areas (CMAs) of Saskatoon and Regina were 2 of these GAs. Each of the 3,289 patients was categorized according to the GAs in which the patient lived at the time of diagnosis. To quantify how rural a GA was, we derived a remoteness score for each GA as the average of the Statistics Canada remoteness indices that were assigned to the residence code boundaries

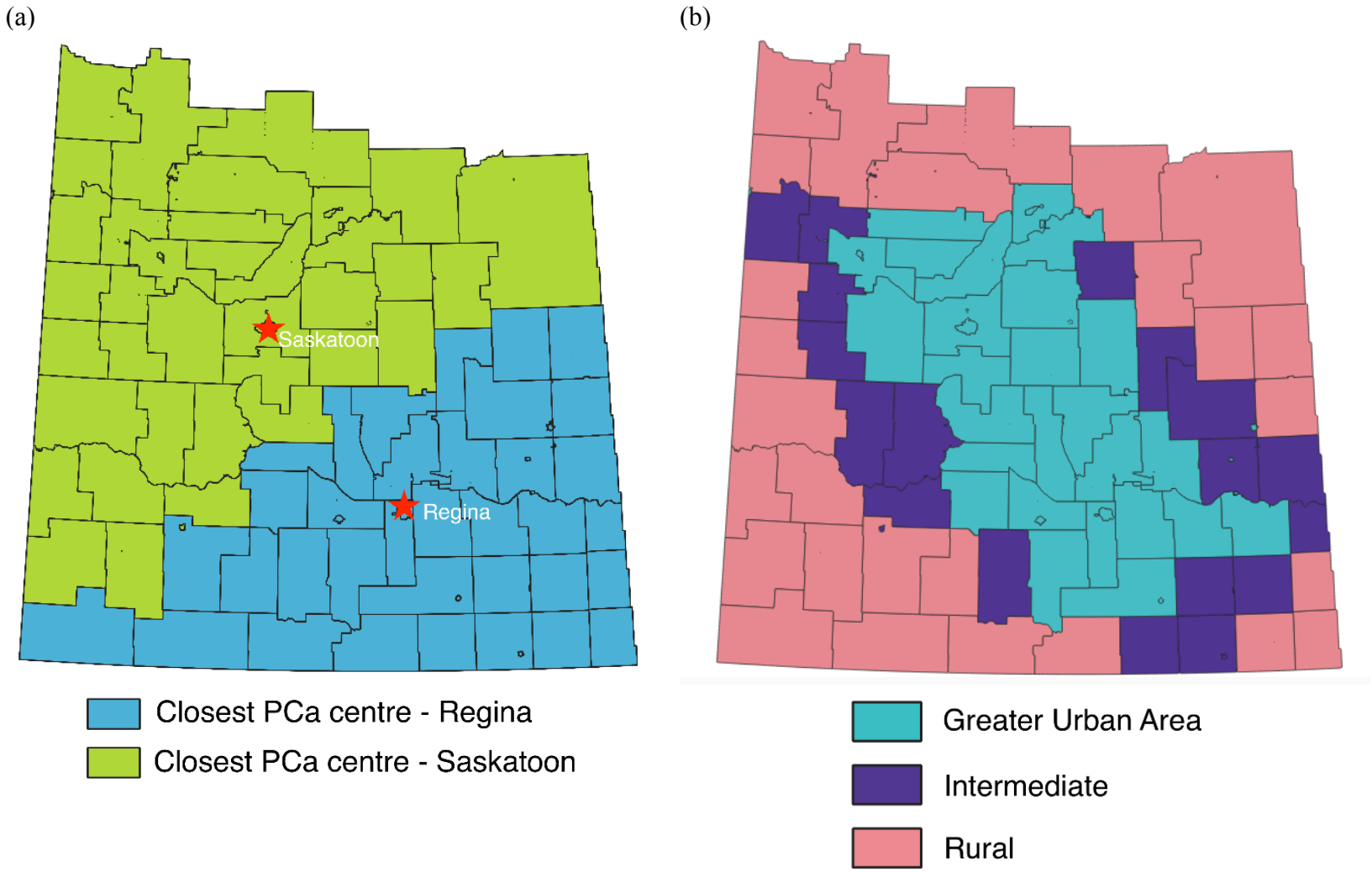

Figure 4.1. The geographic distributions for each of the variables of interest: (A) closest PCa assessment centre to a GA, and (B) GA remoteness index.

forming the GA (21). The GA remoteness index accounts for the following 2 factors: population size and proximity to all population centres (21).

For each GA, we defined its GA remoteness index as "greater urban area," "intermediate remote," or "rural" depending on whether the remoteness score of the GA was less than 0.35, 0.35 to less than 0.40, and 0.40 or more, respectively (21). The criteria are based on the range provided for CMAs and small-size geographies from Statistics Canada remoteness indices (see Figure 4.1) (21). "Greater urban area" consists of Saskatoon and Regina (which have the treatment centres), and their immediate surrounding areas (a GA remoteness index less than 0.35) (21). Geographic regions labeled "intermediate remote" generally consists of smaller cities in the study areas. "Rural" generally consists of GAs (with a GA remoteness index above 0.40) with no small or large city (21).

For each patient, we defined the "closest PCa assessment centre to a GA" in Saskatchewan as Regina or Saskatoon, based on the minimum Euclidean distance between the centroids of the GA of the patient and the 2 cities (see Figure 4.1).

In each model we controlled for the following factors: age at diagnosis, year of diagnosis, risk levels as defined by the Genitourinary Radiation Oncologists of Canada (GUROC), and other treatment types (except in the AS/WW model) (22). Patients with metastatic cancer and those who could not be assigned a GUROC risk level were respectively categorized as "metastatic" and "unknown." Refer to Table 4.1 and Table 4.2 for a summary of the outcome variables, study variables, and covariates.

4.2.3. Statistical Methods

Due to the small sample size, we were unable to develop models for CT treatment utilization. For each of the other 4 treatment outcomes -- AS/WW, RT, Surgery, and HT -- we developed 2 multivariable models as follows.

4.2.3.1. Covariate Models

For each treatment outcome, a multilevel generalized linear model using a binomial link was developed. Using manual backward elimination, we formed the "covariate model" which only contained factors that were statistically significant or confounding. Hence we assessed if

there is any relationship between each of the factors we are studying and each of the treatments. A statistical significance of a factor means it is associated with the given PCa treatment utilization behavior. The covariate model, for each treatment outcome, was the one with the lowest Akaike's information criterion (AIC) value; alpha was set at 0.05 (23). The confounding effect was assessed using a 10% change in the estimated effects of the other independent variables (24).

Each covariate model used the GAs of where patients reside as the random intercept. The value of the random intercept for each GA was used to estimate the proportion of variation unexplained by the factors (25, 26). The effect of where people live (i.e., the random intercept) on the treatment choice was estimated using the intraclass correlation (ICC) (25, 27). Model diagnostics performed comprised: assessing the group-level residuals for any deviation from normality, assessing the outliers of the models using deviance residuals, and assessing the sensitivity and specificity of the models using receiving operating characteristic (ROC) curves.

4.2.3.2. Clustering Analysis

Geographical clustering analysis was conducted using the group-level residual values for each GA from the covariate models (26). This clustering analysis was conducted to assess whether patients within a GA chose a particular treatment more than (or less than) the patients living in the neighbouring GAs. The clustering analysis included assessing the existence of spatial autocorrelation using Global Moran's I, and smaller geography clusters were identified using Local Moran's I. The statistical significance for Global Moran's I was calculated using 999 permutations. If significant, it means that the GAs sharing common boundaries have similar group-level residual values or similar treatment utilization trends instead of random geographical distribution of treatment utilization behavior (26, 28). An inverse distance-based neighbourhood spatial weight matrix with a 120-km cutoff was used to identify local clusters. This weight matrix was chosen to reflect the suspected correlation structure of the data (29). The weight matrix identifies which GAs are neighbours.

4.2.3.3. Full Models

For each treatment, the full model was formed by adding the 2 study variables (GA remoteness index and closest PCa assessment centre to a GA) to the covariate model. This

analysis would tell us whether GA remoteness index and closest PCa assessment centre to a GA were associated with a given treatment utilization behavior, after controlling for other individual factors. The same model building methods and diagnostics described for the covariate models (i.e., step 1) were applied to the full models. The effects of the 2 study variables were compared with the clusters identified in step 2 for any complementary trends. Two-way interaction between the variables of interest (GA remoteness index and closest PCa assessment centre to a GA) was explored in all 4 models.

The multilevel models were built in Stata/IC 15.1 for a Mac (StataCorp LLC, College Station, Texas) using the `melogit` command with the mvaghermite integration method using 12 integration points. The Euclidean distances to the nearest CMA were determined using quantum Geographical Analysis System (QGIS.org) Version 3.4.0-Madeira. Global and Local Moran's I tests were conducted using Geoda 1.12.1.129 (Center for Spatial Data Science, University of Chicago, Illinois).

4.3. Results

4.3.1. Descriptive Statistics

Among all patients, the largest proportions were 60 to 69 years old (38.0%) and 70 to 79 years old (26.8%). In terms of risk levels, intermediate (32.1%) and high risk (33.1%) levels accounted for two-thirds of the cases. The closest PCa assessment centre to a GA for just over half (53.1%) of the patients was in the CMA of Regina. About a third (30.8%) of the patients were categorized as living in the intermediate or rural areas. The utilization of AS/WW at initial diagnosis was just over a quarter of the patients (27.3%). The utilization of RT (31.8%), surgery (30.6%), or HT (34.8%) treatments were each about a third of the patients (see Table 4.1 and Table 4.2 for further descriptive statistics).

4.3.2. Covariate Models

In all 4 models, the year of diagnosis was not statistically significant, increased the AIC values, and did not have a confounding effect. Hence a patient's year of diagnosis did not influence the treatment they chose. The ICC for the random intercept was highest for the RT model (5.7%; $P < 0.0001$) followed by the AS/WW model (1.6%; $P = 0.0006$). The random

intercepts for the surgery ($P = 0.1027$) and HT ($P > 0.9999$) covariate models were not statistically significant. Hence the location of where patients reside may influence their RT and AS/WW treatment decisions, but not their surgery and hormone therapy decision. Ultimately, this is showing that location influences treatment choices. Next, using clustering analysis, we identified which areas in Saskatchewan were more likely to undergo RT and AS treatments.

Table 4.1. Descriptive statistics of all variables in Chapter 4 (n=3289).

Variable	Count (%)	Variable	Count (%)
Treatments[a]		Age groups	
RT	1046 (31.8)	<60	624 (19.0)
Surgery	1005 (30.6)	60 to 69	1250 (38.0)
HT	1146 (34.8)	70 to 79	882 (26.8)
AS/WW	899 (27.3)	80 or above	533 (16.2)
GA Remoteness Index		Closest PCa Assessment Centre to a GA	
Greater Urban Area	2276 (69.2)	Saskatoon	1542 (46.9)
Intermediate	427 (13.0)	Regina	1747 (53.1)
Rural	586 (17.8)		
GUROC risk		Year of diagnosis	
Metastasized	402 (12.2)	2010	606 (18.4)
High	1089 (33.1)	2011	710 (21.6)
Intermediate	1056 (32.1)	2012	724 (22.0)
Low	444 (13.5)	2013	622 (18.9)
Unknown	298 (9.1)	2014	627 (19.1)

[a]Patients may utilize more than 1 treatment within 2 years of diagnosis (between RT, surgery, and HT).

4.3.3. Clustering Analysis

The Global Moran's I for the RT treatment shows evidence of positive spatial autocorrelation (Moran's I = 0.327; pseudo $P < 0.001$). The Local Moran's I shows "low-low" clusters (a group of GAs in which a given treatment is chosen less often than the average) and "high-high" clusters (a group of GAs in which a given treatment is chosen more often than the average). Overall, the RT treatment revealed high-high clusters near the CMA of Saskatoon and low-low clusters near the CMA of Regina (see Figure 4.2). There were also outliers in these high-high and low-low cluster regions known as "low-high" and "high-low." The GAs with a lower-than-average uptake of a treatment that neighbour a GA with a higher-than-average uptake are called "low-high" whereas the vice-versa scenario is called "high-low." Therefore, areas proximal to Saskatoon were more likely to utilize RT treatment.

The Global Moran's I for the AS/WW treatment also showed evidence of positive spatial autocorrelation (Moran's I = 0.091, pseudo $P = 0.026$). The cluster analysis for the AS/WW covariate model showed a reverse trend to that for the RT treatment, meaning high-high clusters near the CMA of Regina and low-low clusters near the CMA of Saskatoon (see Figure 4.2). Therefore, areas proximal to the CMA of Regina were more likely to utilize AS/WW treatment.

Table 4.2. Measure of association between variables of interest and the covariates.

	GA Remoteness Index			Closest PCa Assessment Centre to a GA	
	Greater Urban Area	Intermediate	Rural	Saskatoon	Regina
Age		$P = 0.052$		$P = 0.071$	
<60	462	67	95	284	340
60 to 69	860	164	226	598	652
70 to 79	610	115	157	389	493
80 or above	344	81	108	271	262
GUROC risk		$P = 0.076$		$P < 0.001$	
Metastasized	259	64	79	**235**	167*
High	739	143	207	524	565
Intermediate	756	125	175	501	555
Low	308	51	85	163*	**281**
Unknown	214	44	40	119*	179
Year of diagnosis		$P = 0.753$		$P = 0.319$	
2010	429	76	101	280	326
2011	501	89	120	320	390
2012	484	97	143	354	370
2013	429	88	105	279	343
2014	433	77	117	309	318
RT		$P = 0.047$		$P < 0.001$	
Yes	721	119*	**206**	**612**	434*
No	1555	308	380	930*	**1313**
Surgery		$P < 0.001$		$P < 0.001$	
Yes	**745**	132	128*	422*	**583**
No	1531	295	458	1120	1164
HT		$P < 0.001$		$P < 0.001$	
Yes	742*	162	**242**	**629**	517*
No	1534	265	344*	913*	**1230**
AS/WW		$P = 0.698$		$P < 0.001$	
Yes	616	124	159	339*	**560**
No	1660	303	427	**1203**	1187*

Bold is more than expected
* is less than expected

Since the random intercept for the surgery and HT models were not significant, their group-level residuals were not analyzed.

4.3.4. Full Models

Age and risk levels were strongly associated with each of the treatments (see Table 4.3 for results). For the AS/WW and HT treatments, increase in age increased the odds of utilization for both treatments. In contrast, RT and surgery were most common among younger men (with lower odds as men get older). AS/WW, RT, surgery, and HT were most common among low-risk, intermediate-risk, high-risk, and metastatic patients, respectively. The association between each of the treatments with age and risk levels are visualized in Figure 4.3.

In the final models, the ICC for the random intercept was only significant for the RT model (1.5%; $P = 0.0233$). The random intercepts for the surgery ($P > 0.9999$), AS/WW ($P > 0.9999$), and HT ($P > 0.9999$) full models were not statistically significant.

4.3.4.1. Radiation Therapy

The effect of GA remoteness index on RT treatment utilization depends on which PCa assessment centre the patient lives near (Saskatoon or Regina) (see Tables 4.4 and 4.5 for interaction results). Among patients whose closest PCa assessment centre to a GA was Saskatoon, those living in the greater urban areas had 2.07 (95% CI: 1.22-3.49; $P = 0.007$) times higher odds of RT treatment utilization compared to those living in the intermediate remote areas, but there was no difference in the RT treatment utilization between greater urban and rural areas ($P = 0.307$). Therefore, patients living in the intermediate remote areas were least likely to utilize RT treatment in the GAs where Saskatoon was the closest PCa assessment centre. Among patients whose closest PCa assessment centre was Regina, those living in the greater urban areas had 1.66 (95% CI: 1.03-2.68; $P = 0.039$) times higher odds of RT treatment utilization compared to those living in the rural areas. Hence patients living in the rural areas were least likely to utilize RT treatment in the GAs where Regina was the closest PCa assessment centre. Within the greater urban areas and rural areas, those patients whose closest PCa assessment centre was Saskatoon (compared to Regina) had 2.58 times (95% CI: 1.55-4.31; $P < 0.001$) and 1.89 times (95% CI: 1.36-2.65; $P < 0.001$) higher odds of RT treatment utilization, respectively. Therefore,

in both rural and urban areas, patients whose closest centre was Saskatoon were more likely to utilize RT treatment compared to patients whose closest centre was Regina.

Table 4.3. Odds ratios (with confidence intervals) of independent variables in the full models.

	AS/WW	HT	RT	Surgery
Age groups	***	***	***	***
<60	0.21 (0.15-0.30)*	0.42 (0.28-0.63) *	10.27 (6.83-15.46)*	8.18 (5.82-11.48)*
60 to 69	0.31 (0.23-0.41)*	0.62 (0.44-0.87) *	9.12 (6.30-13.18)*	5.19 (3.83-7.03)*
70 to 79	0.41 (0.31-0.55)*	0.94 (0.68-1.30)	5.78 (4.02-8.30)*	2.07 (1.51-2.85)*
80 or above	Ref. cat.	Ref. cat.	Ref. cat.	Ref. cat.
GUROC risk	***	***	***	***
Metastasized	0.28 (0.20-0.41)*	61.57 (41.31-91.77)*	0.06 (0.04-0.09)*	1.14(0.76-1.71)
High	0.33 (0.26-0.42)*	11.75 (8.83-15.63)*	0.55 (0.42-0.72)*	4.01 (3.14-5.12)*
Intermediate	Ref. cat.	Ref. cat.	Ref. cat.	Ref. cat.
Low	7.83 (6.08-10.10)*	0.15 (0.08-0.27)*	0.34 (0.25-0.45)*	0.11 (0.08-0.16)*
Unknown	3.07 (2.31-4.09)*	0.42 (0.20-0.87)*	0.06 (0.03-0.12)*	1.16 (0.86-1.58)
RT	-	***	-	***
Yes	-	10.01 (7.64-13.10)*	-	0.16 (0.12-0.20)*
No	-	Ref. cat.	-	Ref. cat.
Surgery	-	***	***	-
Yes	-	Ref. cat.	Ref. cat.	-
No	-	6.17 (4.64-8.22)*	6.14 (4.70-8.03)*	-
HT	-	-	***	***
Yes	-	-	9.68 (7.33-12.78)*	0.20 (0.15-0.26)
No	-	-	Ref. cat.	Ref. cat.
GA Remoteness Index			Interaction between GA remoteness index and closest PCa centre to a GA – see Table 4.4 and 4.5 for details	*
Greater Urban Area	Ref. cat.	Ref. cat.		Ref. cat.
Intermediate	1.15 (0.87-1.52)	1.27 (0.92-1.75)		0.95 (0.73-1.25)
Rural	1.14 (0.89-1.48)	1.27 (0.97-1.66)		0.59 (0.45-0.77) *
Closest PCa assessment centre to a GA	*			
Saskatoon	Ref. cat	Ref. cat		Ref. cat.
Regina	1.47 (1.17-1.84)*	0.96 (0.77-1.19)		0.96 (0.80-1.17)

* $P < 0.05$

*** $P < 0.0001$

- Not included in the model because not applicable

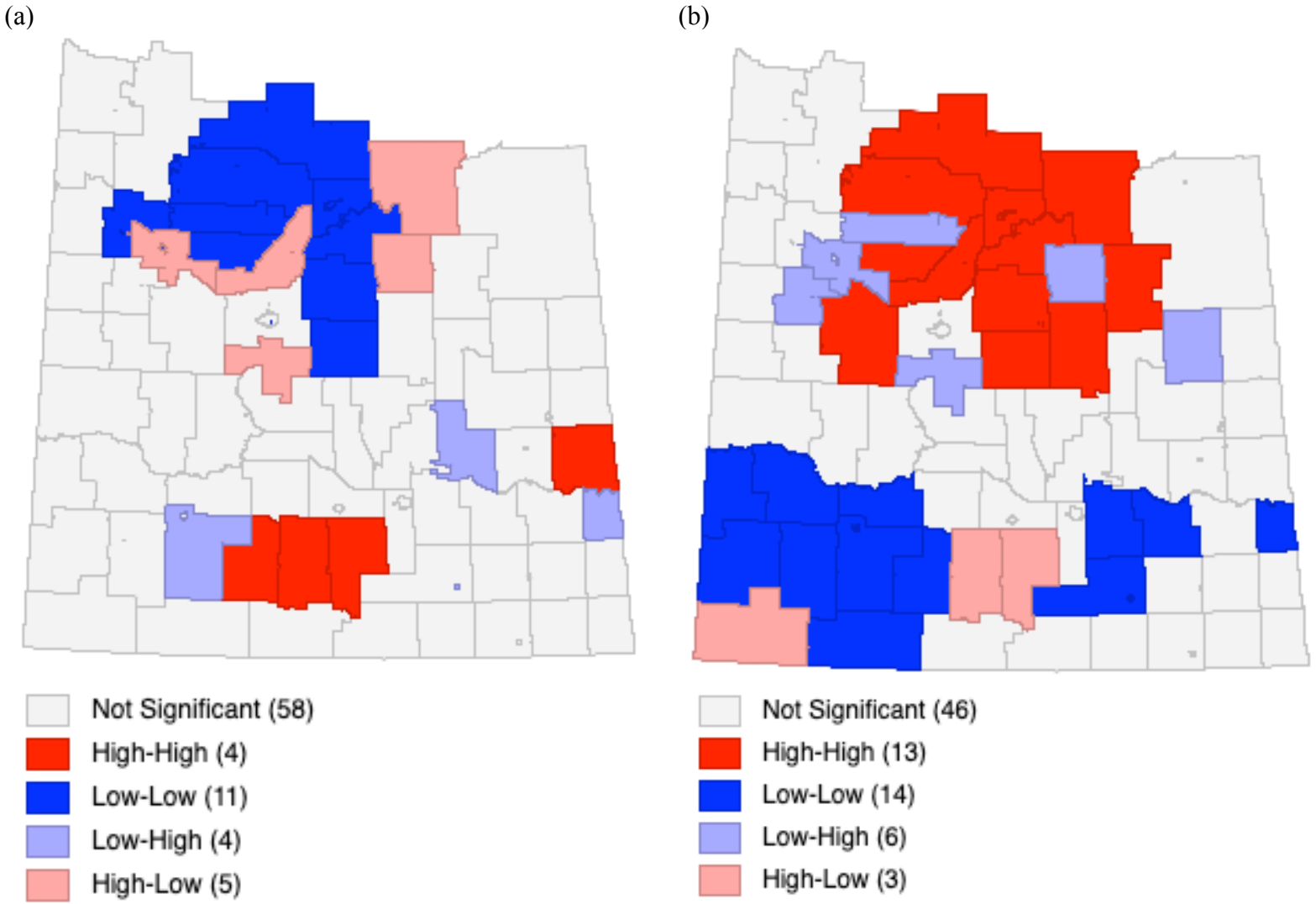

Figure 4.2. Cluster analysis (Local Moran's I test) of group-level residuals for the covariate models using inverse distance weight with cut-off at 120 KM for: (A) active surveillance/watchful waiting treatment, and (B) radiation therapy treatment.

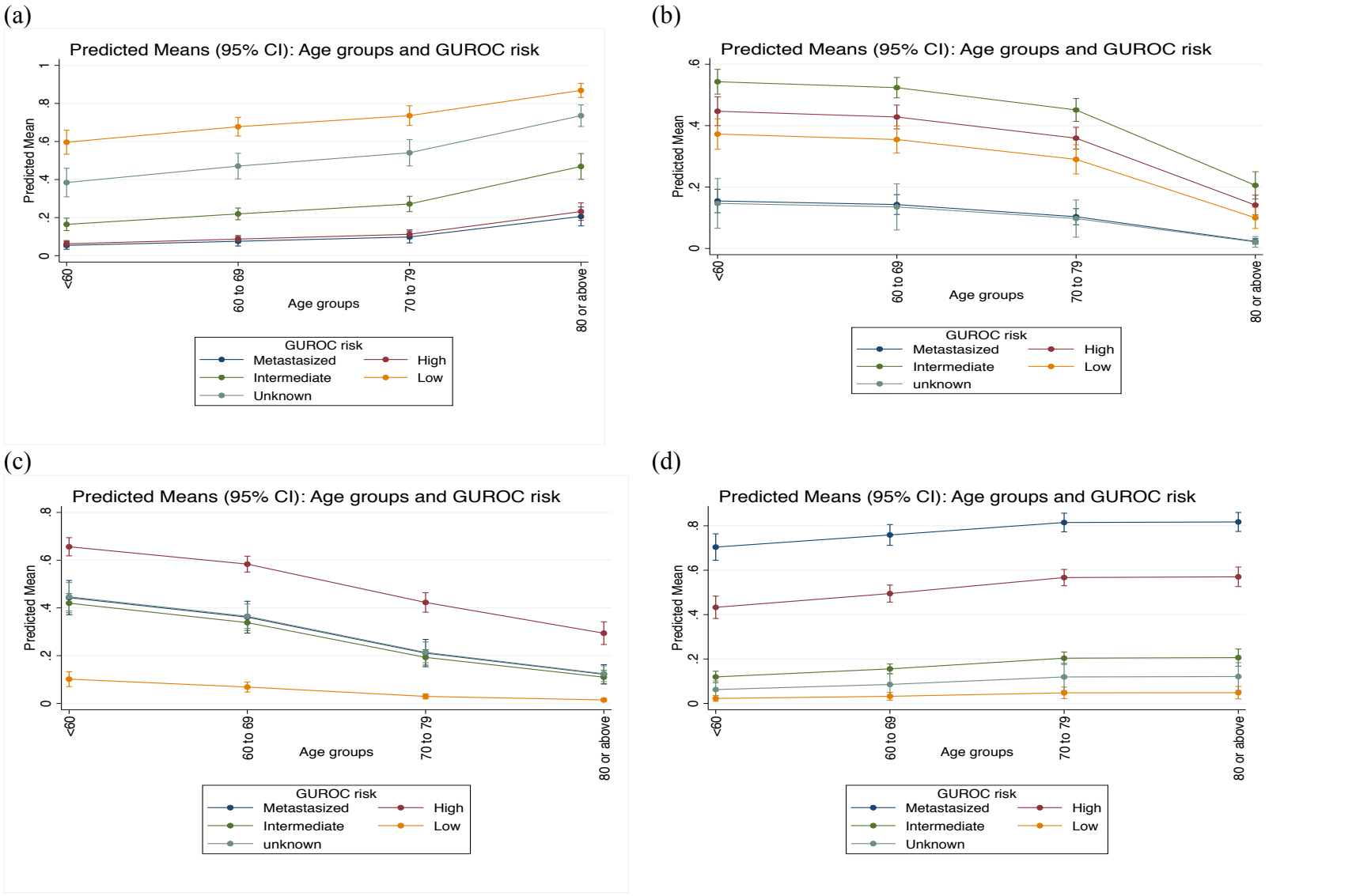

Figure 4.3. Age and GUROC risk levels: Association to each of the treatment options (A) active surveillance/watchful waiting, (B) radiation therapy, (C) surgery, and (D) hormonal therapy.

The effect of the random intercept on the RT model was estimated using the population-averaged odds ratio (see Table 4.6). The population-averaged odds ratios did not statistically differ from the median odds ratios because of the small value of the ICC.

4.3.4.2. Surgery

Those who live in the rural areas had 0.59 (95% CI: 0.45-0.77; $P < 0.001$) times the odds of surgery treatment utilization compared to those living in the greater urban areas (see Table 4.4). Hence patients living in rural areas were least likely to utilize surgery. In terms of the closest PCa assessment centre to a GA (Saskatoon or Regina), there was no difference in the odds of surgery treatment utilization among these 2 groups ($P = 0.709$).

Table 4.4. Odds ratios (with confidence intervals) of interaction effect variables (remoteness index and closest PCa assessment centre) in the radiation therapy full model.

	Coefficient (95% CI)	**OR (95% CI)**	***P***
GA Remoteness Index			0.02
Greater Urban Area	Ref. cat.	Ref. cat.	
Intermediate	-0.73 (-1.25 to -0.20)	0.48 (0.29-0.82)	0.01
Rural	-0.19 (-0.57-0.18)	0.82 (0.57-1.20)	0.31
Closest PCa Assessment Centre to a GA			< 0.01
Saskatoon	Ref. cat.	Ref. cat	
Regina	-0.64 (-0.97 to -0.30)	0.53 (0.38-0.74)	< 0.01
GA Remoteness Index x Closest PCa Assessment Centre to a GA			0.03
Intermediate x Regina	0.77 (0.07-1.47)	2.17 (1.08-4.37)	0.03
Rural x Regina	-0.31 (-0.92-0.30)	0.73 (0.40-1.34)	0.32

4.3.4.3. Active Surveillance or Watchful Waiting

The effect of GA remoteness index on AS/WW treatment utilization was found to be not statistically significant. Therefore, AS/WW utilization rates did not change regardless of whether patients lived in rural or urban areas. However, those living closest to the Regina PCa assessment centre had 1.47 (95% CI: 1.17-1.84) times the odds of AS/WW treatment utilization compared to those living closest to the Saskatoon PCa assessment centre (see Table 4.4). Hence patients whose closest centre was Regina were more likely to utilize AS/WW compared to patients whose closest centre was Saskatoon.

Table 4.5. Select pairwise contrasts between GA remoteness index and closest PCa assessment centre to a GA for the radiation therapy full model.

	Contrast (95% CI)	OR (95% CI)	*P*
Greater Urban Area vs. Rural			
Closest PCa assessment centre – Regina	0.51 (0.02-0.99)	1.66 (1.03-2.68)	0.04
Closest PCa assessment centre – Saskatoon	0.19 (-0.18-0.57)	1.22 (0.84-1.77)	0.31
Greater Urban Area vs. Intermediate			
Closest PCa assessment centre – Regina	-0.05 (-0.50-0.40)	0.95 (0.61-1.50)	0.84
Closest PCa assessment centre – Saskatoon	0.73 (0.20-1.25)	2.07 (1.22-3.49)	0.01
Intermediate vs. Rural			
Closest PCa assessment centre – Regina	0.55 (-0.01-1.12)	1.74 (0.99-3.06)	0.06
Closest PCa assessment centre – Saskatoon	-0.53 (-1.09-0.02)	0.59 (0.34-1.03)	0.06
Closest PCa assessment centre – Saskatoon vs. Closest PCa assessment centre - Regina			
Rural	0.95 (0.44-1.46)	2.58 (1.55-4.31)	< 0.01
Intermediate rural	-0.13 (-0.74-0.47)	0.87 (0.48-1.60)	0.66
Greater Urban Area Saskatoon vs Regina	0.64 (0.30-0.97)	1.89 (1.36-2.65)	< 0.01

Table 4.6. The effect of random intercept (median odds ratios and population average odds ratios) in the radiation therapy full model.

	Coefficient (Median)	Coefficient (Population Averaged)	Odds Ratios (Median)	Odds Ratios (Population Averaged)
Age groups				
<60	2.33	2.31	10.27	10.07
60 to 69	2.21	2.19	9.12	8.94
70 to 79	1.75	1.74	5.78	5.69
80 or above	Ref. cat.	Ref. cat.	Ref. cat.	Ref. cat.
GUROC risk level				
Metastasized	-1.71	-1.69	0.18	0.18
High	0.49	0.48	1.63	1.62
Intermediate	1.09	1.08	2.97	2.94
Low	Ref. cat.	Ref. cat.	Ref. cat.	Ref. cat.
Unknown	-1.79	-1.77	0.17	0.17
Surgery				
Yes	Ref. cat.	Ref. cat.	Ref. cat.	Ref. cat.
No	1.82	1.80	6.14	6.05
HT				
Yes	2.27	2.25	9.68	9.49
No	Ref. cat.	Ref. cat.	Ref. cat.	Ref. cat.

4.3.4.4. Hormonal Therapy

The effect of GA remoteness index on HT treatment utilization was found to be not statistically significant. In addition, there was no statistical difference in HT treatment utilization

among those living closest to Regina or Saskatoon PCa assessment centres. Hence both GA remoteness index and closest PCa assessment centre to a GA did not influence HT treatment utilization.

4.4. Discussion

This is first such study in Saskatchewan, of which we are aware, that investigates the relationship between closest PCa assessment centre to a GA, GA remoteness index, and treatment utilization for PCa. This study found that patients living in the rural parts of Saskatchewan have lower odds of choosing surgery compared to patients living in greater urban areas. While surgery may seem appealing to some patients living in rural areas due to the logistics of one-time travel, this study shows that patients living in rural areas are still less likely to undergo surgery (30). A similar trend has been observed in the United States and Australia where rural dwellers were less likely to undergo surgery for their PCa, which the authors of these studies attributed to the longer travel distance to the centralized urban treatment centres, access to health care providers, and the geographical differences in the management of patients (13, 14, 31-34). Given that PCa surgery in Saskatchewan is also centrally administered in the CMAs of Regina and Saskatoon, living in rural parts of the study area may be a proxy for needing longer travel to the Saskatchewan PCa assessment centres (compared to greater urban areas) (35). Studies on rural patients in British Columbia (another western Canadian province) found that long distance to urban health centres was a substantial barrier for cancer care due to travel expenses (36, 37). Other personal factors that may influence decisions for rural patients include rural cultures and attitudes of feeling marginalized in urban health care centres, and consequently avoiding treatments (7).

For the RT treatment option, the effect of urban-rural disparity depends on the closest treatment centre for the patients. Among rural patients that had Saskatoon as their closest PCa assessment centre, there was no difference in choosing RT compared to the greater urban area. However, there is a cluster of patients living in the "intermediate remote" region that have Saskatoon as their proximal PCa assessment centre with lower odds of undergoing RT than patients living in the greater urban area. This study also found that the odds of choosing RT to be much greater among those whose closest PCa assessment centre was Saskatoon compared to

Regina (for both rural and urban areas). In the literature, the findings are mixed as well; whilst in British Columbia there was no difference in the utilization of RT between urban and rural PCa patients, in Ontario and Australia, studies from the late 1990s found RT treatment utilization was more common in areas near the treatment centres than those areas that were farther away (8, 38, 39). A possible reason for lower odds of RT treatment among rural patients that have Regina as their closest PCa assessment centre could be due to the burden of daily travel over several weeks that is needed for RT (30). Other possible reasons identified in Canada could be the perceptions of long waits for RT, leading to either patients refusing treatment or physicians not making referrals (40). In addition, patients living in rural areas may have less access to specialists with adequate knowledge of RT treatments (8). The difference in RT treatment utilization between Saskatoon and Regina regions may possibly be due to difference in AS/WW trends (discussed in the next paragraph).

This study found that patients whose closest PCa assessment centre was Regina have higher odds of choosing AS/WW compared to Saskatoon. The spatial analysis shows complementary results, with clusters in southern Saskatchewan near the CMA of Regina. If AS/WW is considered as a treatment option to delay curative treatment, this could suggest that patients in certain parts of southern Saskatchewan might be delaying their curative treatment more than in the GAs where Saskatoon is the closest PCa assessment centre. Comparing the AS/WW results to the RT results, we find that the region with higher odds for AS/WW is the same region with lower odds for RT (GAs whose closest PCa assessment centre is Regina). These disparities may be due to different physician practices or possible health access issues that are unique to the southern and central regions of Saskatchewan. Further research is required to identify the underlying reasons for the regional disparities for RT utilization in Saskatchewan. For HT, there was no difference in choosing HT regardless of the closest PCa assessment centre to a GA or the GA remoteness index. A study in the United States also showed no difference in AS/WW and HT utilization between rural and urban dwellers, similar to our study (41). This may be due to the availability of HT treatment (medication) because medications could be directly mailed to the patients.

In terms of individual factors that were controlled for, this study shows older age and low-risk PCa are associated with increased odds of choosing AS/WW. AS/WW is a non-curative

treatment, and other studies also show it is most common among patients who are older, have greater comorbidities, and have low-risk PCa (42, 43). The PCa treatment guidelines identify AS/WW as a suitable option for low risk PCa and patients with less than 10 years of life expectancy (44-46). For intermediate and high risk patients, RT is considered a suitable a suitable option or surgery may be considered for patients with greater than 10 years of life expectancy (44-46). The treatment guidelines identify HT as a standard of care for all metastatic PCa patients (44-46). Hence, the findings of this study also align with the treatment guidelines, which shows the use of AS/WW was most commonly among patients with low-risk PCa (44-46). Undergoing HT was most common among older men, those who also had RT treatment utilization, and those who had high risk or metastatic PCa. Since HT is considered to improve treatment outcomes for those who are high risk or metastatic, and if they are undergoing RT, the findings are promising and consistent with what we may expect (47-49). Given the highest odds of HT was among metastatic patients, the findings of this study show Saskatchewan treatment trends for metastatic PCa align with the treatment guidelines (44-46). For RT and surgery, the utilization was higher among younger men, which is consistent with findings in another study looking at age as a factor for treatment utilization trends in Canada (50). In addition, our study shows RT and surgery were most commonly administered among intermediate and high risk PCa patients, which is consistent with the treatment guidelines (44-46). This study also shows that patients who received RT treatment were also commonly treated with HT, which aligns with the treatment guidelines (44-46). Hence, this study shows that treatment use patterns (among Saskatchewan patients with different risk levels) align with the expected clinical treatment guidelines (44-46).

The potential limitations of this study include the lack of information on other treatment decision factors, including patient preferences, that possibly influence treatment choice (51). Data on patient comorbidity were also not available. This study was not able to distinguish those who were on watchful waiting versus active surveillance due to the nature of the population-level data. Consequently, AS/WW may include individuals who were unmanaged for PCa treatment. For HT, the data only capture drug-based treatments.

4.5. Conclusions

Overall, there are regional disparities for PCa treatment utilization in Saskatchewan. Living in rural and remote areas affects surgery treatment utilization and, in some geographical areas, affects RT. For non-curative treatments (i.e., AS/WW and HT), we did not find any association with geographical remoteness. However, we did find regional disparity for AS/WW depending on the closest PCa assessment centre for the patient's geographical area. Further research is required to identify the underlying reasons for the regional disparities for surgery, RT, and AS/WW utilization in Saskatchewan.

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CHAPTER 5 – GEOGRAPHIC FACTORS ASSOCIATED WITH TIME-TO-TREATMENT OUTCOMES FOR RADIATION THERAPY AMONG LOCALIZED PROSTATE CANCER PATIENTS IN SASKATCHEWAN

Article reproduced with permission and minor edits. Originally published as: Andkhoie M, Szafron M. Geographic factors associated with time-to-treatment outcomes for radiation therapy among localized prostate cancer patients in Saskatchewan. *J Cancer Policy*. 2020; 26; https://doi.org/10.1016/j.jcpo.2020.100259. My contributions to this study include data acquisition, study design, data analysis, interpretation of findings and manuscript preparation.

In this chapter, we present the complete study used to address the research question "Are the PCa time-to-treatment outcomes in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?" associated with our first study objective "to determine the associations (if any) between components of healthcare access and each of PCa incidence, treatment usage and time-to-treatment trends among Saskatchewan patients". Specifically, in this chapter we assess factors associated with 'ready-to-treat'-to-treatment (RTTx) time and diagnosis-to-treatment time for radiation therapy (RT) among prostate cancer (PCa) patients. These factors include remoteness level of where patients live and the closest PCa assessment centre. Multivariable analyses were conducted using zero-inflated negative binomial and Poisson regression models for the RTTx and diagnosis-to-treatment times, respectively. RT diagnosis-to-treatment time is positively correlated with the remoteness-index ($P < 0.001$). RTTx time differences between the Saskatoon and Regina areas exist but only among intermediate and low-risk cases. Among all intermediate risk and low risk patients, those in the Saskatoon area had 1.76 (95% CI: 1.38, 2.25; $P < 0.001$) and 2.15 (95% CI: 1.16, 3.98; $P = 0.015$), respectively, times longer RTTx times compared to patients in the Regina area. Those patients living in the Saskatoon area had 1.08 (95% CI: 1.01, 1.16; $P = 0.035$), 1.15 (95% CI: 1.04, 1.28; $P = 0.009$) and 1.64 (95% CI: 1.24, 2.16; $P < 0.001$) times longer RT diagnosis-to-treatment times compared to patients living in Regina area among high, intermediate and low risk patients, respectively. There was a decrease in diagnosis-to-treatment time between 2011 and 2014 compared to 2010 ($P < 0.001$). We show that living in rural/remote areas is associated with delays for PCa RT. Both RTTx and diagnosis-to-treatment times for PCa RT were longer in localized regions in Saskatchewan where Saskatoon was the closest PCa assessment centre. There was a decrease in RT delays between 2010 and 2014 in

Saskatchewan. Policies addressing treatment delays should ensure localized strategies for rural/remote areas to reduce geographic disparities in time-to-treatment outcomes.

5.1. Introduction

In Canada, prostate cancer (PCa) is estimated to be the third leading cause of all cancer deaths (after lung and colorectal cancers) among men (1). Within Canada, Saskatchewan has the highest projected age-standardized PCa mortality rate (29.8 deaths per 100,000 in 2019) compared to all other provinces (1). Although it is not known what factors are leading to such high mortality rates in Saskatchewan, because delays to PCa treatments are known to adversely affect biochemical outcomes for high-risk PCa patients, in this study we explore waiting and delay factors possibly impacting PCa treatments in Saskatchewan (2-5). While there are four main types of PCa treatments (active surveillance/watchful waiting, surgery, radiation therapy (RT) and hormonal therapy), in this study we focus on RT (6).

For RT, the Canadian Association of Radiation-Oncologists (CARO) has set a target wait-time of 14 days (7). However, the length of the wait-times varies by province (8). In 2013, Saskatchewan had reported wait-times of 27 days (for 90% of their PCa patients initiating RT), hence more work is needed to achieve the CARO wait-time target of 14 days (8).

Looking at the PCa treatment centre availability in Saskatchewan, RT is centrally administered in two cities: Regina and Saskatoon (9). Consequently, nearly half of the Saskatchewan population (who live outside of these two cities) would commute to these two cities for treatment (10). Long commutes are a known barrier for patients living in the rural and remote areas of Saskatchewan (11, 12). In terms of RT for PCa, there are no known studies regarding the association between rural residence and wait-times in Saskatchewan. However, research from Australia shows cancer patients living in rural areas face longer delays for treatment compared to their urban counterparts (13, 14). Literature also shows patients living in rural regions have lower survival rates for cancers when compared to patients living in urban regions (15-19). Therefore, we hypothesize that patients living in remote regions of Saskatchewan face longer waiting periods for their PCa RT treatment. Two waiting periods of interest here are the ‘ready-to-treat’ to treatment period and the diagnosis-to-treatment period.

Our first objective is to determine the association (if any) between PCa patient 'ready-to-treat' to treatment times for RT and the following factors: the remoteness level of where patients live; the closest PCa assessment centre for the patient; and other factors including patient's age, risk levels, number of initial treatments and year of diagnosis. The second objective is to assess whether there is an association between the PCa patient diagnosis-to-treatment times for RT and the aforementioned factors.

5.2. Methods

5.2.1. Definitions

Localized PCa is defined to be patients with low, intermediate and high risk levels based on the definitions of Genitourinary Radiation Oncologists of Canada (GUROC) (20). The initial treatment is defined as undergoing RT within 2 years of diagnosis (21). The Saskatchewan Cancer Agency defines the 'ready-to-treat' date as "the day on which the patient is ready to receive treatment, taking into account clinical factors and patient preference" (22). The 'ready-to-treat'-to-treatment time is defined to be the time between the "ready-to-treat" date and the initial treatment start date for RT (21). The diagnosis-to-treatment time is defined as the time between the diagnosis date and the initial treatment start date for RT (23).

5.2.2. Data

The Saskatchewan Cancer Registry (SCR) is a database for cancer patients diagnosed or treated in Saskatchewan. The study population were residents in the SCR from south central Saskatchewan who were diagnosed with localized PCa and received RT within Saskatchewan between 2010 and 2014. While the SCR contained information for 774 localized PCa patients undergoing RT (as initial treatment) within the study population, the study used data from 701 patients (90.8%), after excluding patients living out-of-province at the time of diagnosis (36 cases; 4.6%), those living in the three (17 cases; 2.2%) former northern health regions (Mamawetan Churchill River, Keewatin Yatthe, and Athabasca), and those patients with missing "ready-to-treat" date (20 cases; 2.3%). Those living in the northern health regions were excluded for privacy reasons because these health regions could not be subdivided into smaller geographical areas (GAs). The impact of excluding missing data was assessed using Little's Test

for Missing Completely At Random (24, 25). The University of Saskatchewan BioMedical Research Ethics Board provided ethics approval (Bio-REB certificate #15-34).

5.2.3. Outcome Variables

5.2.3.1. 'Ready-to-treat'-to-treatment (RTTx) time

For the RTTx time, we computed the variable as: difference in the number of weeks between the date of "ready-to-treat" and date of RT treatment initiation (Figure 5.1) (21). In the literature, RTTx time is also termed as "wait-time" for RT and reported to be measured in days or weeks and we chose to use weeks as the unit of measure in this study (26, 27). Individuals with RTTx time values less than zero (that is, negative values) were deemed to be data entry errors and were excluded from the dataset (<10 cases). We considered fewer than five cases (with RTTx time greater than 30 weeks) to be extreme outliers because the RTTx time for all other cases ranged from 0 to 14 weeks. After removing these outliers, the final dataset consisted of 692 patients.

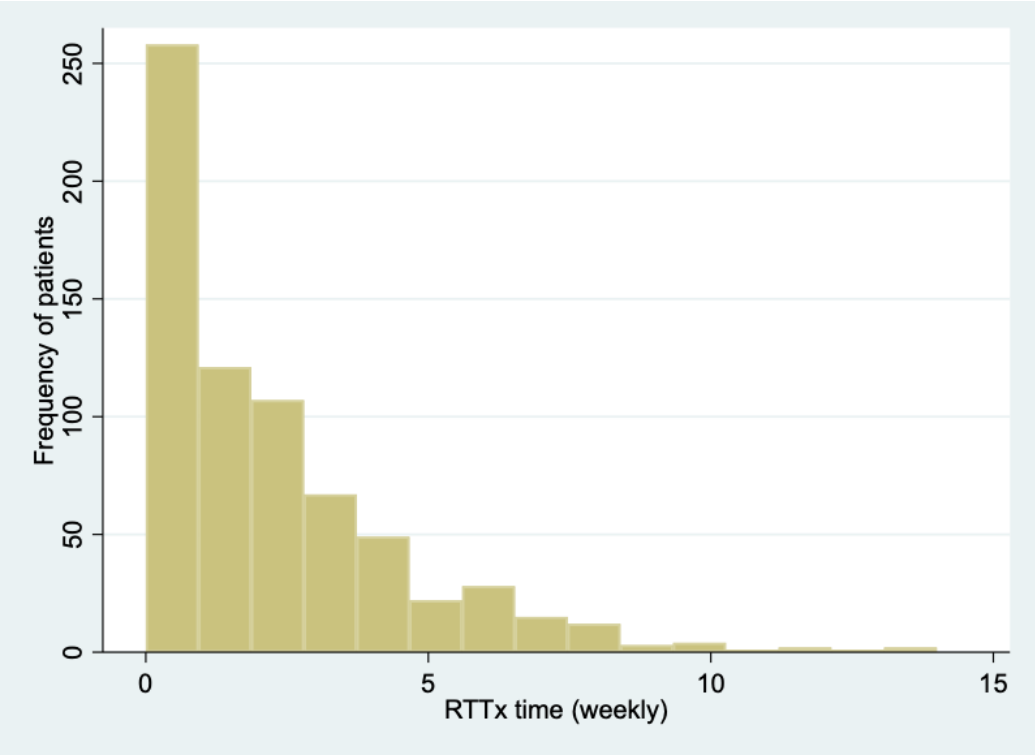

Figure 5.1. 'Read-to-treat' to treatment (RTTx) time for radiation therapy (weekly).

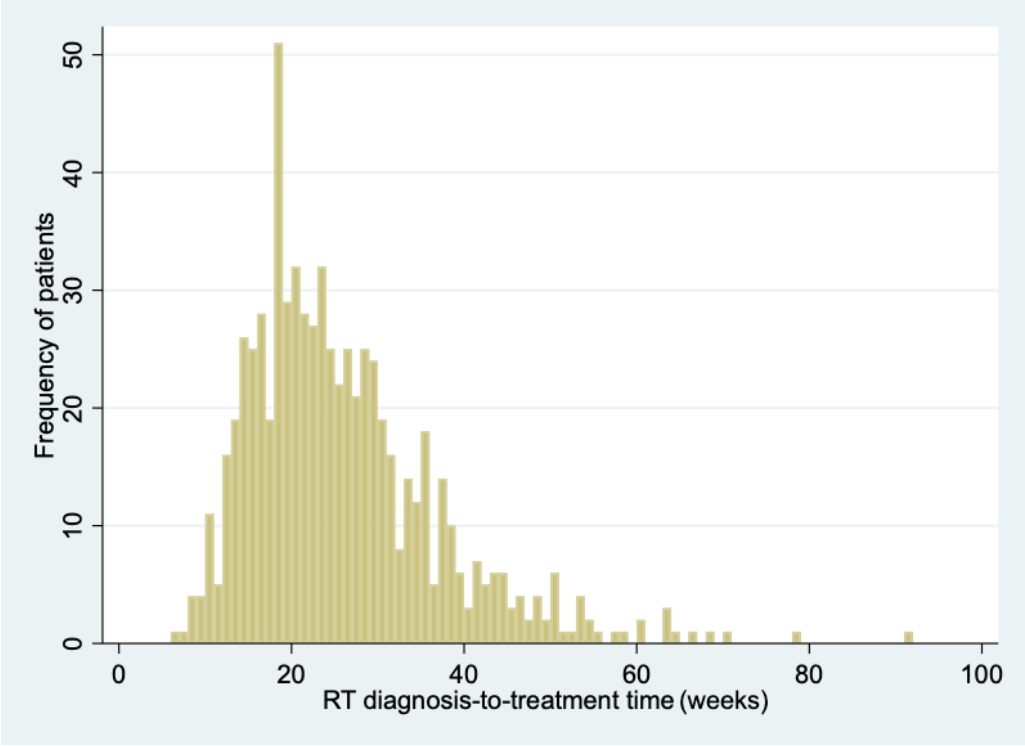

Figure 5.2. Diagnosis-to-treatment time for radiation therapy (weekly).

5.2.3.2. RT diagnosis-to-treatment time

For the RT diagnosis-to-treatment time, we computed the variable as: difference in the number of weeks between the date of PCa diagnosis and date of RT treatment initiation (23). For consistency, the RT diagnosis-to-treatment time variable is also measured in weeks (Figure 5.2).

5.2.4. Independent Variables

The SCR subdivided central and southern Saskatchewan into 82 GAs using residence code boundaries for privacy reason (Figure 5.3 and Figure 5.4) (28). The cities of Saskatoon and Regina were two of these GAs (Figure 5.3 and Figure 5.4). Each of the 692 patients was categorized per the GA in which the patient lived at the time of diagnosis.

To quantify how rural a GA was, we derived a remoteness score (a continuous variable) for each GA as the average of the Statistics Canada remoteness indices that were assigned to the residence code boundaries forming the GA (29). The GA remoteness index accounts for the following two factors: population size, and proximity to all population centres (29). The GA remoteness index ranged from 0.22 to 0.50 in the GAs in the study area. In general, major cities

in Saskatchewan and their surrounding areas have a GA remoteness index of less than 0.35. The GAs with no cities have a score of over 0.40 (in Saskatchewan, cities are defined to have a population of 5,000 or more) (30). The remoteness of each GA is illustrated in Figure 5.3.

For each patient, we defined the "closest PCa assessment centre to a GA" in Saskatchewan as Regina or Saskatoon based on the minimum Euclidean distance between the centroids of the GA of the patient and the two cities (Figure 5.4). Those GAs that have Saskatoon as their closest PCa assessment centre are classified as the "Saskatoon area" and those GAs that have Regina as their closest PCa assessment centre are assigned as the "Regina area".

Because each patient had at least RT in the two years following diagnosis, we determined the number of PCa treatments for a patient to be: "1" if the patient only received RT; "2" if the patient received RT and one more treatment (surgery or hormonal therapy; grouped because of the small sample size if coded separately); and "3" if the patient received all three treatments (RT, surgery and hormonal therapy).

The other variables included were age, year of diagnosis and risk levels as defined by GUROC (20).

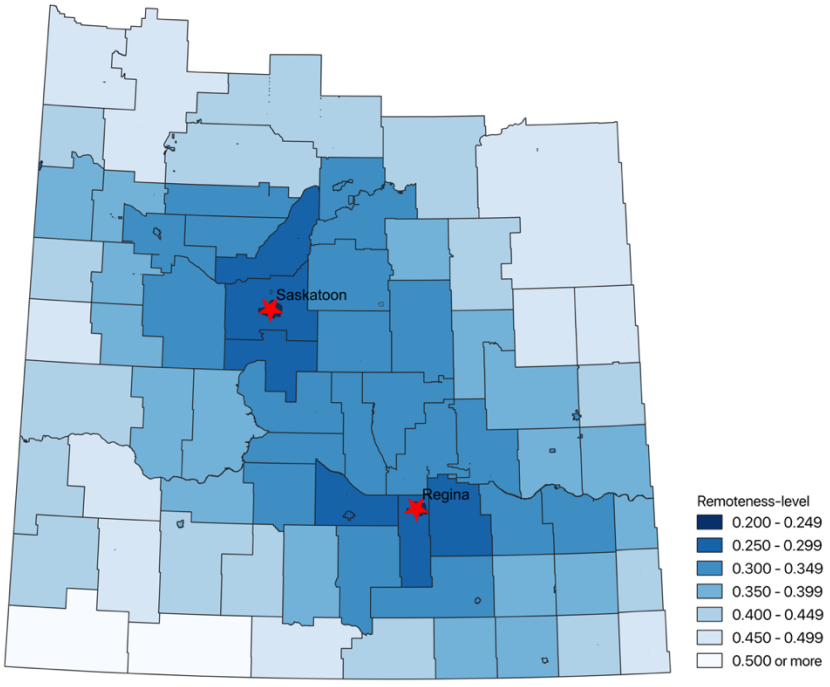

Figure 5.3. Remoteness index for each geographic area in Saskatchewan.

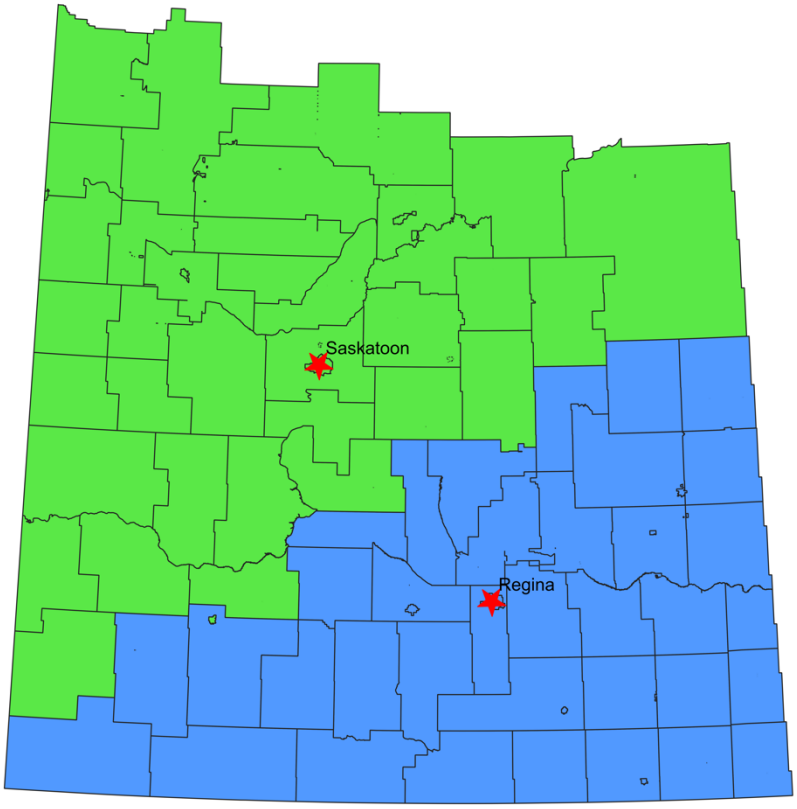

Figure 5.4. Closest PCa assessment centres of Saskatoon (green) and Regina (blue) for each of the geographic areas in Saskatchewan.

5.2.5. Statistical Methods

Based on the distribution of the RTTx time variable, non-parametric independent sample tests (Mann Whitney U two sample statistic and Kruskal-Wallis equality-of-population rank test) were conducted to assess any differences in the medians and distributions of the RTTx and diagnosis-to-treatment times by each variable of interest (31-34).

In terms of multivariable analysis, Poisson regression analysis was considered due to the count nature of both outcome variables (35). Due to the variance of RTTx times being much larger than the mean of RTTx times, as well as lack of model fit (using goodness-of-fit test), a negative-binomial regression model was built (35, 36). Next, due to the large number of zero-values (37%) in the RTTx times, a zero-inflated negative model was also built (35). The best of these two models was assessed using the Akaike's Information Criterion (AIC) (37). The zero-inflated negative model was used due to the improved model fit (reduction of more than 2 units

in the AIC value) (37). For the RT diagnosis-to-treatment time, Poisson regression analysis was deemed the better model via the same process described for the RTTx time model. The diagnosis-to-treatment model additionally controlled for RTTx time because the length of RTTx time could affect the diagnosis-to-treatment time.

The first step in the multivariate analysis was an unconditional analysis of each independent variable with the outcome. All the independent variables with p-value<0.20 (in the unconditional analysis) formed the initial multivariate model (38). Then backwards-manual model building was used and the best model was chosen based on the lowest AIC value; alpha was set at 0.05 (37). A confounding effect was assessed using a 10% change in the estimated effects of the other independent variables (39). Two-way interactions between the significant fixed-effect factors were identified based on a post-hoc Wald test and a reduction in AIC value (reduction of 2 units or more) (37, 40).

Model diagnostics were conducted using deviance residuals, and we assessed the linearity of independent continuous variables to the linearized outcome by refitting the final models as a Box-Tidwell regression model (41, 42). Note that the final models were also built using "days" as the unit for RTTx times and diagnosis-to-treatment times, to determine the impact on the results.

Descriptive statistics, non-parametric analysis, Poisson and negative binomial modeling, and Box-Tidwell regression (for diagnostics) were conducted in Stata/IC 15.1 for a Mac. The Euclidean distances were computed using quantum Geographical Analysis System (QGIS) Version 3.4.0-Madeira. Due to the availability of model diagnostics, the zero-inflated negative binomial models were built in R version 3.6.2 using the `zeroinfl` command within the "pscl" package (43).

5.3. Results

The RTTx time for 37% of the patients (258 patients) was 0 days. Half of the patients (median RTTx time) were treated within 1 week. Nine out of ten patients (90th percentile) were treated within 5 weeks. The interquartile range (IQR) of the RTTx time was 3 weeks and the range was 0 to 14 weeks.

For RT diagnosis-to-treatment time, the median was 23 weeks and the 90th percentile was 40 weeks. The IQR of the diagnosis-to-treatment time was 12.5 weeks and the range was 6 weeks to 92 weeks. See Table 5.1 for detailed descriptive statistics.

5.3.1. Non-parametric Analysis

For the RTTx times, the Kruskal-Wallis tests show that the distributions for the following independent variables were different: GUROC risk levels and number of treatments (Table 5.2). To identify which categories within these independent variables had different medians, the Mann Whitney U tests were conducted. The median RTTx time for high-risk cases (1 week) was significantly lower than median RTTx time for intermediate-risk (2 weeks; $P < 0.0001$) and low-risk cases (2 weeks; p-value = 0.008).

For the RT diagnosis-to-treatment times, the Kruskal-Wallis tests showed that the distributions for the following independent variables were different: GUROC risk levels, closest PCa assessment centre to a GA, and number of treatments (Table 5.2). Based on the Mann Whitney U tests, the median diagnosis-to-treatment time for high-risk cases (26 weeks) was significantly higher than median diagnosis-to-treatment time for intermediate-risk (19 weeks; $P < 0.0001$) and low-risk (18 weeks; $P < 0.0001$). The median diagnosis-to-treatment time for patients in the Regina area (20.5 weeks) was significantly lower than median diagnosis-to-treatment time for those patients in the Saskatoon area (25 weeks; $P < 0.0001$).

5.3.2. Multivariable Analysis

The multivariable models using days as the time unit had statistically consistent results with models using weeks as the time unit; hence for the sake of simplicity and comparing models, we only present the models using weeks.

5.3.2.1. ‘Ready-to-treat’-to-treatment time

In the RTTx time model, age and GA remoteness index were not included in the final model because they were not statistically significant and did not have a confounding effect. The final model consisted of year of diagnosis, number of treatments, risk levels and closest PCa assessment centre to a GA. In addition, we found a significant interaction effect between risk levels and the closest PCa assessment centre to a GA.

Table 5.1. Descriptive statistics for 'ready-to-treat' to treatment (RTTx) time and diagnosis-to-treatment time outcomes (n=692).

		RTTx time		Diagnosis-to-treatment time	
	n	Median	90th percentile	Median	90th percentile
Total	692	1 week	5 weeks	23 weeks	40 weeks
Independent variables					
Age					
<60	97	1 week	5 weeks	23 weeks	42 weeks
60 to 69	285	1 week	5 weeks	24 weeks	41 weeks
70 to 79	279	1 week	6 weeks	23 weeks	38 weeks
80 or above	31	1 week	6 weeks	21 weeks	37 weeks
GUROC risk levels					
Low	35	2 weeks	7 weeks	18 weeks	35 weeks
Intermediate	253	2 weeks	6 weeks	19 weeks	37 weeks
High	404	1 week	4 weeks	26 weeks	43 weeks
Year of diagnosis					
2010	136	1 week	5 weeks	26 weeks	47 weeks
2011	135	1 week	7 weeks	23 weeks	38 weeks
2012	163	1 week	6 weeks	23 weeks	35 weeks
2013	120	1 week	4 weeks	22.5 weeks	42 weeks
2014	138	1.5 weeks	6 weeks	21 weeks	37 weeks
Closest PCa assessment centre to a GA					
Regina area	312	2 weeks	4 weeks	20.5 weeks	38 weeks
Saskatoon area	380	1 week	6 weeks	25 weeks	41 weeks
Number of treatments					
1	164	3 weeks	7 weeks	16 weeks	27 weeks
2	479	1 week	4 weeks	25 weeks	39 weeks
3	49	2 weeks	5 weeks	35 weeks	60 weeks
Type of treatments*					
RT only	164	3 weeks	7 weeks	16 weeks	27 weeks
RT and surgery	43	2 weeks	4 weeks	31 weeks	45 weeks
RT and hormonal therapy	436	1 week	4 weeks	24 weeks	38 weeks
RT, surgery and hormonal therapy	49	2 weeks	5 weeks	35 weeks	60 weeks

Independent variable "GA remoteness index" not shown because it is not a factor variable.
*Not an independent variable. Included as a descriptor for "Number of treatments".

In terms of year of diagnosis, between 2010 and 2014, those patients diagnosed in 2013 had the shortest RTTx time. In terms of the number of treatments, the RTTx times for those patients with two treatments were 0.576 (95% CI: .452, 1.93; $P < 0.001$) times the RTTx times for those patients with one treatment. See Table 5.3 and Figure 5.5 for details.

Table 5.2. Non-parametric results - Kruskal-Wallis equality-of-populations rank test chi-square value and statistical significance.

	RTTx time		Diagnosis-to-treatment time	
	Chi-square	P	Chi-square	P
Age	0.543	0.9093	2.98	0.3942
GUROC risk levels	15.5	0.0004	73.9	0.0001
Year of diagnosis	3.38	0.4960	13.4	0.0095
Closest PCa assessment centre to a GA	0.524	0.4691	27.3	0.0001
Number of treatments	72.4	0.0001	168	0.0001

Independent variable "GA remoteness index" not shown because it is not a factor variable.

Table 5.3. Multivariable analysis results - incidence rate ratios (IRR) for fixed effect variables in the RTTx time and diagnosis-to-treatment models.

RTTx time model

	IRR (95% CI)	***P***
Year of diagnosis		< .001
2010	Ref. cat.	
2011	1.22 (.954, 1.56)	.112
2012	.930 (.732, 1.18)	.553
2013	.682 (.519, .895)	.006
2014	1.02 (.796, 1.30)	.889
Number of treatments		< .001
1	Ref. cat	
2	.576 (.452, .733)	< .001
3	.717 (.491, 1.05)	.085

RT diagnosis-to-treatment model

	IRR (95% CI)	***P***
Year of diagnosis		< .001
2010	Ref. cat.	
2011	.885 (.845, .927)	< .001
2012	.853 (.815, .892)	< .001
2013	.862 (.821, .905)	< .001
2014	.784 (.748, .822)	< .001
Number of treatments		< .001
1	Ref. cat	
2	1.52 (1.45, 1.61)	< .001
3	2.23 (2.08, 2.40)	< .001
GA Remoteness index	1.45 (1.21, 1.75)	< .001
RTTx time	1.02 (1.01, 1.03)	< .001

Table 5.4. Select pairwise contrasts for the interaction variables (GUROC risk levels and closest PCa assessment centre to a GA) for the RTTx time multivariable model.

	RTTx time model		
	Contrast (95% CI)	IRR (95% CI)	P
High risk patients in Saskatoon area vs High risk patients in Regina area	.205 (-.012, .422)	1.23 (0.99, 1.52)	.064
Intermediate risk patients in Saskatoon area vs Intermediate risk patients Regina area	.565 (.322, .809)	1.76 (1.38, 2.25)	<.001
Low risk patients in Saskatoon area vs Low risk patients in Regina	.764 (.148, 1.38)	2.15 (1.16, 3.98)	.015

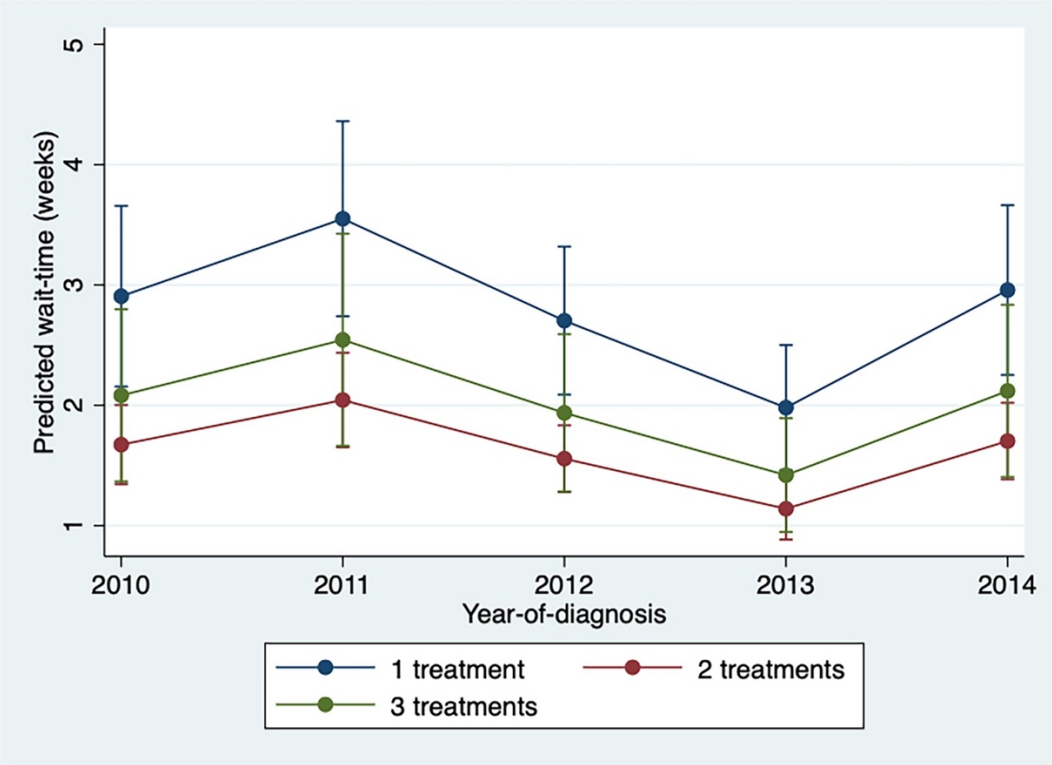

Figure 5.5. Predicted RTTx time stratified by year of diagnosis and number of treatments.

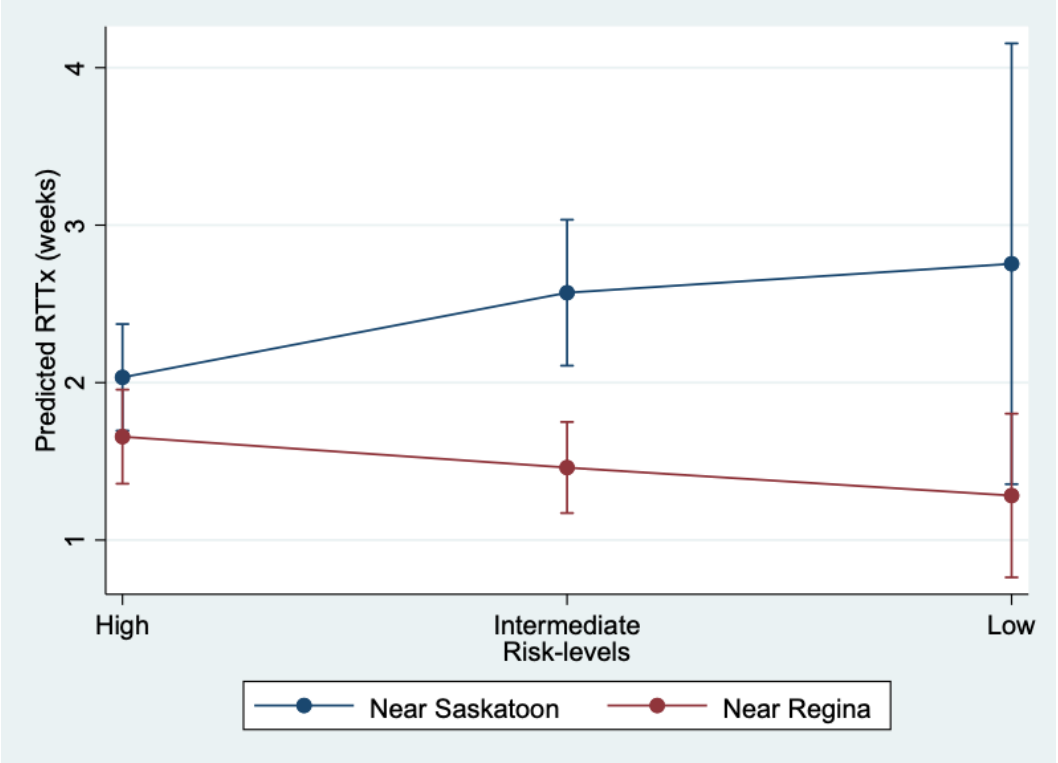

Figure 5.6. Interaction between GUROC risk level and closest PCa assessment centre to a GA in the RTTx time model.

The RTTx time differences between the Saskatoon and Regina areas exist but only among intermediate and low-risk cases. Among all intermediate risk patients, those in the Saskatoon area had 1.76 (95% CI: 1.38, 2.25; P < 0.001) times longer RTTx time compared to patients in the Regina area. There was no difference in the RTTx times between the two areas among high-risk level patients (P =0 .064). See Table 5.4 and Figure 5.6 for details.

5.3.2.2. RT diagnosis-to-treatment time

In the RT diagnosis-to-treatment time model, age was not included in the final model because there was no statistical significance and confounding effect. The final model consisted of year of diagnosis, number of treatments, risk levels, GA remoteness index, closest PCa assessment centre to a GA and RTTx time. In addition, like the RTTx time model, we found a significant interaction effect between risk levels and the closest PCa assessment centre to a GA.

In terms of the remoteness variable, RT diagnosis-to-treatment time is positively correlated with GA remoteness index (P < 0.001). Since the coefficient of GA remoteness index is 0.375, therefore an increase of 0.1 unit of GA remoteness index would be equal to an average increase in diagnosis-to-treatment time by 3.8% (Figure 5.7).

The results of year of diagnosis and number of treatments are in Table 5.3 and visualized in Figure 5.8. Overall, there is a decrease in diagnosis-to-treatment time between 2011 and 2014 compared to 2010. For the number of treatments, patients receiving one of either surgery or hormonal therapy with RT had 1.52 times longer diagnosis-to-treatment than those receiving RT only (P < 0.001). Patients receiving both surgery and hormonal therapy with RT had 2.23 times longer diagnosis-to-treatment for receiving RT only (P < 0.001).

Those patients living in the Saskatoon area had 1.08 (95% CI: 1.01, 1.16; P = 0.035), 1.15 (95% CI: 1.04, 1.28; P = 0.009) and 1.64 (95% CI: 1.24, 2.16; P < 0.001) times longer RT diagnosis-to-treatment time compared to patients living in the Regina area among high, intermediate and low risk patients, respectively (Table 5.5 and Figure 5.9).

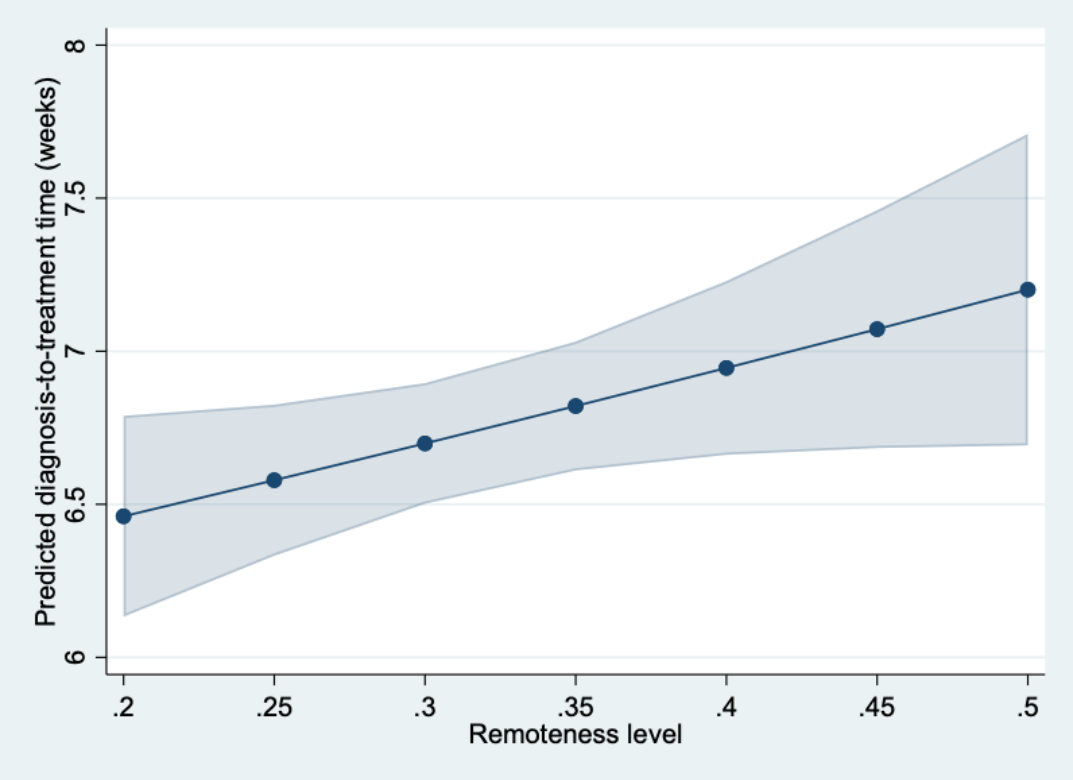

Figure 5.7. Predicted diagnosis-to-treatment time by geographic area remoteness index.

Table 5.5. Select pairwise contrasts for the interaction variables (GUROC risk levels and closest PCa assessment centre to a GA) for the radiation therapy diagnosis-to-treatment model.

	Diagnosis-to-treatment Contrast (95% CI)	IRR (95% CI)	*P*
High risk patients in Saskatoon area **vs** High risk patients in Regina area	.083 (.045, .120)	1.09 (1.05, 1.13)	<.001
Intermediate risk patients in Saskatoon area **vs** Intermediate risk patients Regina area	.153 (.098, .207)	1.16 (1.10, 1.23)	<.001
Low risk patients in Saskatoon area **vs** low risk patients in Regina	.498 (.356, .640)	1.65 (1.43, 1.90)	<.001

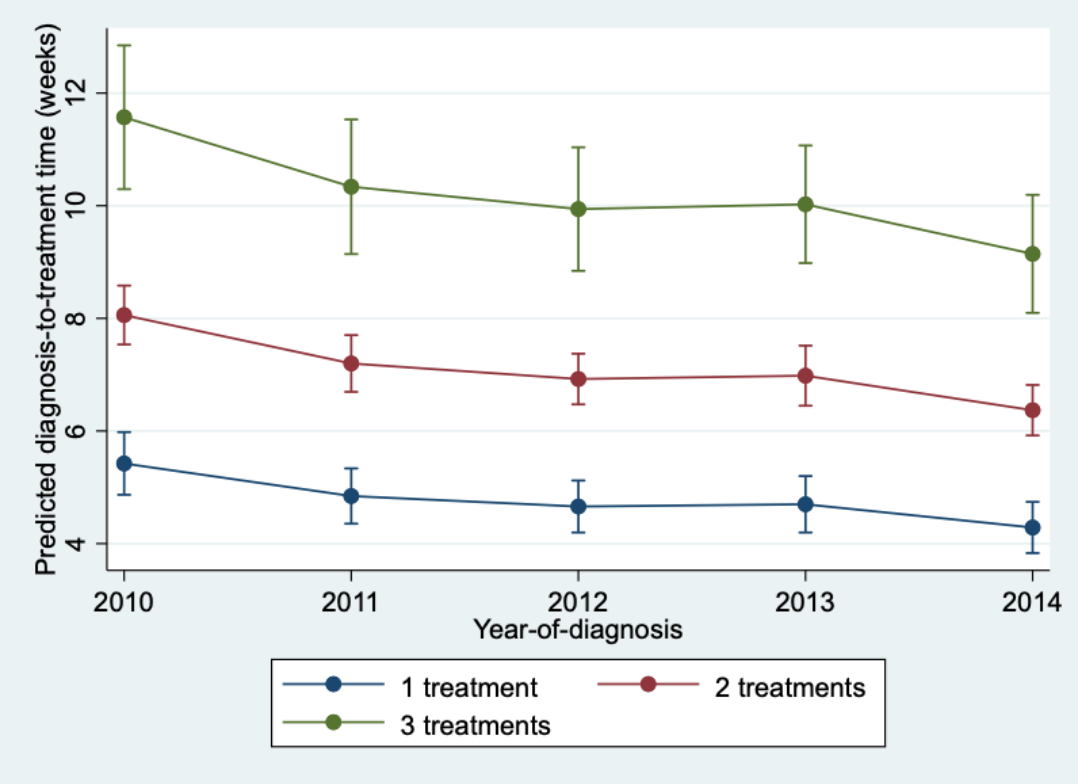

Figure 5.8: Predicted diagnosis-to-treatment time by year of diagnosis and number of treatments.

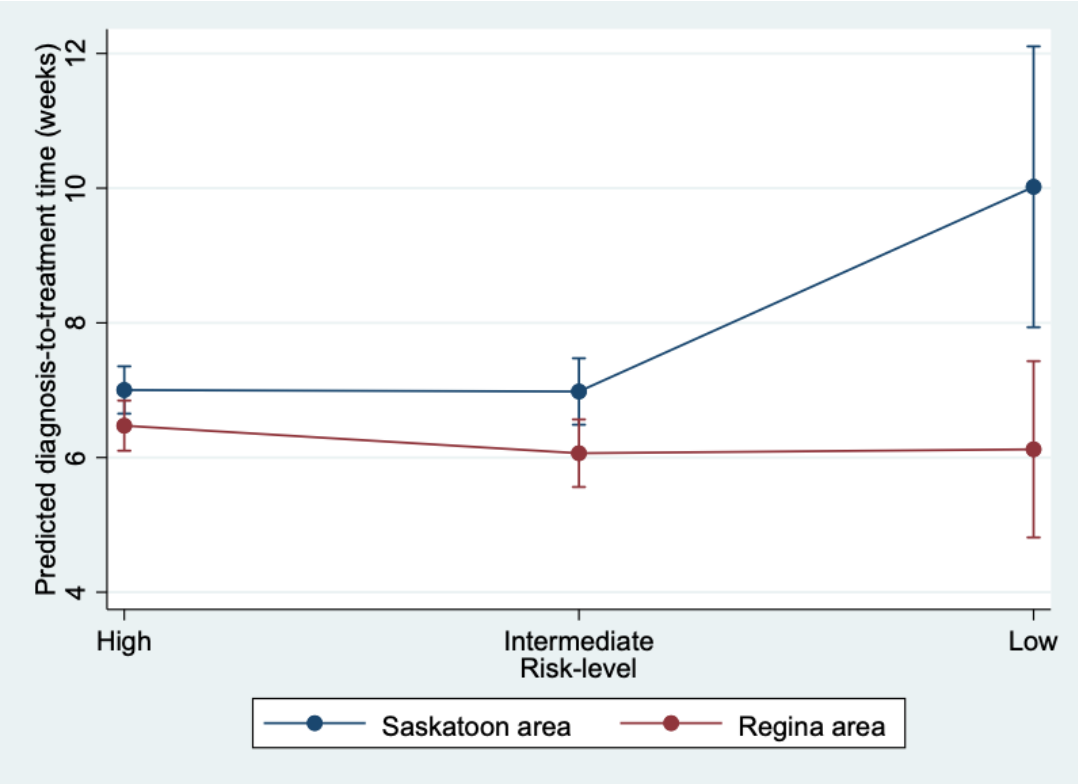

Figure 5.9. Interaction between risk level and closest PCa assessment centre to a GA for the diagnosis-to-treatment model.

5.4. Discussion

This study shows that patients living in remote regions in Saskatchewan have longer diagnosis-to-treatment times for RT, but the RTTx times are not affected by GA remoteness index. Hence patients living in remote regions may face delays (or decide to delay their RT), but once they are in the cancer care system, those living in remote regions have similar RTTx times to those living in urban regions. This is an important finding, as it shows that those living in rural/remote areas are facing certain barriers to delay their RT in Saskatchewan, but once these patients are in the cancer care system, the RTTx times are not affected by where they live. In terms of treatment delays for PCa, to our knowledge, not many studies have assessed its association with remoteness, but studies for other cancer types show similar findings that living in rural areas affect time to treatment, including for colorectal and lung cancers (13, 14). Based on what is known from the international literature, healthcare access issues including travel time and distance, and availability of specialist appointments have been identified as barriers by physicians and patients regarding delays for treatments among rural patients (44, 45). Rural attitudes and cultures have also been identified as possible reasons why patients living in rural and remote areas may delay or face system delays for their treatments (45, 46). Further research is needed to identify if similar reasons are driving the delays in PCa treatment among patients living in remote areas in Saskatchewan.

This study found that both RTTx and diagnosis-to-treatment times are longer in the areas with Saskatoon as the closest PCa assessment centre compared to Regina. A possible reason for the longer RTTx times in the Saskatoon areas is shown in the interaction effect with the risk level groups of the patients. There is difference in the RTTx times between the Saskatoon and Regina areas because those who are intermediate-risk and low-risk wait longer for their treatment in the Saskatoon area. Among high-risk group, there is no difference in the RTTx times between patients living in the two areas. While it is promising that the RTTx times for high-risk groups are similar in the two areas, it is not known why there are RTTx time differences between the two areas for low-risk and intermediate risk PCa patients. We know from a recent report that the median and 90th percentile for RTTx times in Saskatchewan were longest among low-risk groups (8), which is consistent with the findings of this study. A similar finding of longer diagnosis-to-treatment times among low-risk group PCa patients was found in a

recent Canadian study (47). The total volume of RT in Saskatoon was higher than Regina in our data sample, which one may suspect as a potential reason for the difference in the RTTx times between the centres, but further research is needed. Another possible reason could be due to difference in the interpretation of how RTTx is assigned in each of the centres, which requires further research. Future research involving interviews and surveys (mixed methods) of patients and frontline healthcare workers at the two centres could provide possible answers regarding the geographic disparities observed in this study.

The average RTTx in both Saskatoon and Regina for all risk levels were less than three weeks (Figure 5.6). Based on communications with Saskatchewan Cancer Agency, RTTx of three weeks was the established target for 90% of the radiation therapy procedures during the study period in Saskatchewan (47). Although the average RTTx for PCa patients achieved this target (as per multivariable analysis), the 90th percentile (Table 5.1) for RTTx was 5 weeks (2 weeks longer than the establish target), hence further measures might be needed to address the long waits between 'ready-to-treat' date and initial radiation therapy (47).

Based on the multivariable analysis, this study found that patients receiving RT with surgery and/or hormonal therapy have longer diagnosis-to-treatment times. Based on Table 5.1, those who had RT and surgery had longer time to treatment compared to those who had RT and hormonal therapy. In addition, the longer diagnosis-to-treatment times among high-risk PCa in Table 5.1 could possibly be explained by a majority (393 out of 404; 97%) of the "high-risk" PCa patients received RT with surgery and/or hormonal therapy. The multivariable analysis accounted for other factors including the number of treatments, and it showed that high-risk PCa patients had the shorter diagnosis-to-treatment time compared to low risk patients (Figure 5.9).

This study shows that RTTx and the diagnosis-to-treatment times were similar for patients of all age groups. This is consistent with a Canadian study that found no correlation between age and diagnosis-to-treatment time for RT among PCa patients (48). In terms of year of diagnosis, the RT diagnosis-to-treatment time appears to be decreasing over time between 2010 and 2014. The reasons for these reductions is not known and requires further research.

5.5. Conclusions

This study shows that patients living in remote regions in Saskatchewan have longer diagnosis-to-treatment times for RT, but the RTTx times are not affected by remoteness levels. In addition, both RTTx and diagnosis-to-treatment times are longer in the areas with Saskatoon as the closest PCa assessment centre to a GA compared to Regina. There is difference in the RTTx times between the Saskatoon and Regina areas (those who are intermediate-risk and low-risk wait longer for their treatment in the Saskatoon area). Further research is needed to explore the personal reasons for rural and remote PCa patients for delaying their treatments.

5.6. References

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CHAPTER 6 – FACTORS UNDERLYING TREATMENT DECISION-MAKING FOR LOCALIZED PROSTATE CANCER IN THE U.S. AND CANADA: A SCOPING REVIEW USING PRINCIPAL COMPONENT ANALYSIS

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In this chapter, we present the complete study used to address the research question "What factors and corresponding themes in the literature have been identified to affect the treatment decision-making of localized prostate cancer patients in Canada and the United States?" associated with our second study objective "to identify and describe the overarching themes influencing treatment decision-making for localized PCa patients". Specifically, in this chapter we gather, collate, and identify key factors commonly studied in localized prostate cancer (LPC) treatment decision-making in Canada and the U.S. This scoping review uses five databases (Medline, EMBASE, CINAHL, AMED, and PsycInfo) to identify relevant articles using a list of inclusion and exclusion criteria applied by two reviewers. A list of topics describing the themes of the articles was extracted and key factors were identified using principal component analysis (PCA). A word cloud of titles and abstracts of the relevant articles was created to identify complementary results to the PCA. This review identified 77 relevant articles describing 32 topics related to LPC treatment decision-making. The PCA grouped these 32 topics into five key factors commonly studied in LPC treatment decision-making: 1) treatment type; 2) socioeconomic/ demographic characteristics; 3) personal reasons for treatment choice; 4) psychology of treatment decision experience; and 5) level of involvement in the decision-making process. The word cloud identified common phrases that were complementary to the factors identified through the PCA. We identified several possible factors impacting LPC treatment decision-making. Further research needs to be completed to determine the impact that these factors have in the LPC treatment decision-making experience.

6.1. Introduction

Prostate cancer is one of the most commonly diagnosed invasive cancers in Canada and the United States (US) (1-4). Localized prostate cancer (LPC), i.e., cancer contained within the prostate gland, accounts for about 79% of all prostate cancers diagnosed in North America (1). The progression of LPC to the metastatic stage has a substantial negative impact on the relative survival of the patients (the five-year relative survival decreases from 100% to 30%) (1). Therefore, the monitoring of the disease and undergoing necessary treatment(s) are important to prevent metastasis.

The most common treatment types for LPC are active surveillance or watchful waiting (AS/WW), radiation therapy, surgery (prostatectomy), and hormonal therapy (5). Each treatment has different side effects (including incontinence and erectile dysfunction), impacting the quality-of-life for patients and their families (6-8). Therefore, it is necessary for physicians to make sure treatment choices align with patient needs and preferences. Studies on treatment decision-making focus on specific patient profiles, for example, ethnic and racial minorities, different age groups, and specific treatment types (9-16). While there is research describing treatment decision-making for varying LPC patient profiles, there is no literature comprehensively identifying common factors underlying treatment decision-making.

The purpose of this research is to gather, collate and identify key factors commonly studied in LPC treatment decision-making in Canada and the United States.

6.2. Methods

Following the scoping review process of Arksey and O'Malley, we reviewed the literature to identify key factors for LPC treatment decision-making in Canada and the United States (17). The following steps were taken to compile the list of relevant articles:

In step 1, one of the reviewers compiled the list of references from five databases (Medline, EMBASE, CINAHL, AMED and PsycInfo) using the search terms listed in Table 6.1.

In step 2, the same reviewer from step 1 removed the duplicates in the list of references.

Table 6.1. Search terms used in the five databases.

Terms describing prostate cancer	Terms describing treatment decision-making
Prostatic neoplasms	Decision-making
Prostate cancer	Patient preference
Prostatic AND neoplasms	Patient participation
(prostat* adj6 (cancer* or carcinom* or tumor* or tumour* or neoplasm* or adenocarcinom* or intraepithelial))	Decision support techniques
	Preferences
	Client participation
	Decision support systems
	Consumer participation
	Decision making support
	Choice behavior

Table 6.2. Inclusion/exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Peer-reviewed articles	Commentaries, News, Abstracts
English language	Editorials, Case Studies, Reviews
Specific to LPC	Outside designated timeframe
Exclusively regarding LPC	Outside designated country of the corresponding author
Specific to treatment decision-making	Duplicate article
Timeframe: September 1997 to August 2016	
Country of the corresponding author: the US or Canada	

Note: The geographical origin of the article was based on the country of the corresponding author (18).

In step 3, the same reviewer from step 1 removed references outside the inclusion countries/timeframes and references that were not full-text peer-reviewed articles, and compiled a list of peer-reviewed articles.

In step 4, two reviewers independently applied the inclusion/exclusion criteria listed in Table 6.2 to the titles and abstracts of the peer-reviewed articles and compiled a list of full-text review articles.

In step 5, both reviewers independently conducted a full-text article review and applied the inclusion/exclusion criteria to the list compiled in step 4, and compiled a list of relevant articles.

The two reviewers discussed and resolved any disagreements to include/exclude articles in the fourth and fifth steps. The levels of agreement between the two reviewers in fourth and fifth steps were assessed using the Cohen Kappa Statistic.

Two methodologies were then used to identify the key factors commonly studied in LPC treatment decision-making:

First, both reviewers discussed and agreed upon the general topics identified within the relevant articles from step 5. A Principal Component Analysis (PCA) with Promax oblique rotation (loadings greater than 0.275 and less than -0.275 were grouped together) and a parallel analysis (with 1000 Monte Carlo simulation repetitions) were used to identify the underlying LPC treatment decision-making factors from these general topics (19-21).

Second, a word cloud was created as a qualitative approach to identify complementary results to the PCA (first method) using word frequencies in the titles and abstracts of the relevant articles.

All authors discussed and agreed upon the interpretations of the key factors identified. The Cohen Kappa statistic was calculated using IBM SPSS Statistics 22.0. PCA was conducted in Stata IC 12.1. Word Cloud was created in NVivo for Mac 11.4.1.

6.3. Results

In Step 1, the list of references from the five databases contained 1861 items. Next, after duplicates were removed, 1200 articles remained. In Step 3, 559 articles were excluded (details in Figure 6.1) and a list of 641 peer-reviewed articles remained. In Step 4, out of the remaining 641 articles, both reviewers agreed 89 articles needed full-text article review (Cohen's Kappa Statistic 0.789; $p<0.001$). Upon full-text review of these articles, 77 articles were retained (Cohen's Kappa Statistic 0.689; $p<0.001$). Among the retained articles, 55 (71%) were from the US and 22 (29%) from Canada. After the review, 32 general topics studied regarding LPC treatment decision-making were identified and are listed in Table 6.3.

Applying PCA to the 32 identified topics resulted in five overarching factors (see Table 6.3): treatment type, socioeconomic/demographic characteristics, personal reasons for treatment

choice, psychology of treatment decision experience, and level of involvement in the decision-making process, based on the five highest eigenvalues that were generated from the PCA.

Table 6.3: Key factors and their associated general topics extracted from the reviewed relevant articles.

Key Factors	General Topics	Loadings
Treatment types (9-16, 22-65)	Surgery (prostatectomy)	0.4643
	Radiation therapy	0.4093
	Active surveillance/watchful waiting	0.3717
	Brachytherapy	0.3636
	Hormonal therapy	0.2812
Socioeconomic/demographic factors (10, 12, 14, 15, 23-26, 28, 31, 32, 35-37, 41, 43, 44, 46, 48, 53-55, 58, 59, 61-63, 65-70)	Sociodemographic factors	0.4482
	Monetary influences - cost, insurance	0.3944
	Race	0.3688
	Epidemiological studies on decision-making	0.3436
	Age	0.2766
Personal reasons for treatment choice (9-16, 22, 23, 25, 28-37, 40, 41, 43-47, 50, 51, 55-63, 65-67, 70-84)	Personal decision-making factors	0.4479
	Inconvenience and timing	0.3665
	Utilities and side effects	0.3267
	Fear of death/need for cure	0.3227
	Patient-use of decision aids	-0.2893
	Actual or perceived health state/risk	0.2852
Psychology of treatment decision experience (9, 12, 13, 15, 16, 22-24, 26, 27, 29, 30, 32, 33, 35, 36, 39, 41, 43, 44, 46, 49, 51, 52, 55, 57, 59-61, 63, 64, 66, 68-70, 72, 73, 75-77, 79, 81, 83, 85)	Confidence, regret and satisfaction	0.4664
	Stress/difficulty in decision-making	0.4338
	Psychology and coping factors	0.3488
	Marital Status	0.3344
	Post-treatment quality of life	0.3203
Levels of involvement in decision-making (11-13, 15, 16, 22-25, 27-31, 33-46, 48-53, 55, 56, 59-68, 70-90)	Physician role and influence	0.4894
	Shared/informed decision-making: active/passive	0.3808
	Behavior models using economic theories	-0.3649
	Information and knowledge	0.3438
	Partner/family/friend participation and views	0.3038

Note: Principal Component Analysis accounted for six other topics ("spirituality", "multidisciplinary practice", "consulting multiple providers", "discordant decisions", "complementary and alternative medicine", and "health literacy") partially within all five key factors.

Associated with the highest eigenvalue (see Table 6.3 for values), the PCA grouped the LPC treatment type (including surgery and radiation therapy) as an overarching factor. Interestingly, LPC treatment type also emerged as the most frequently mentioned topic in the

word cloud. Therefore, both methodologies complement each other and show "treatment type" as a frequently studied LPC treatment decision-making factor in the literature.

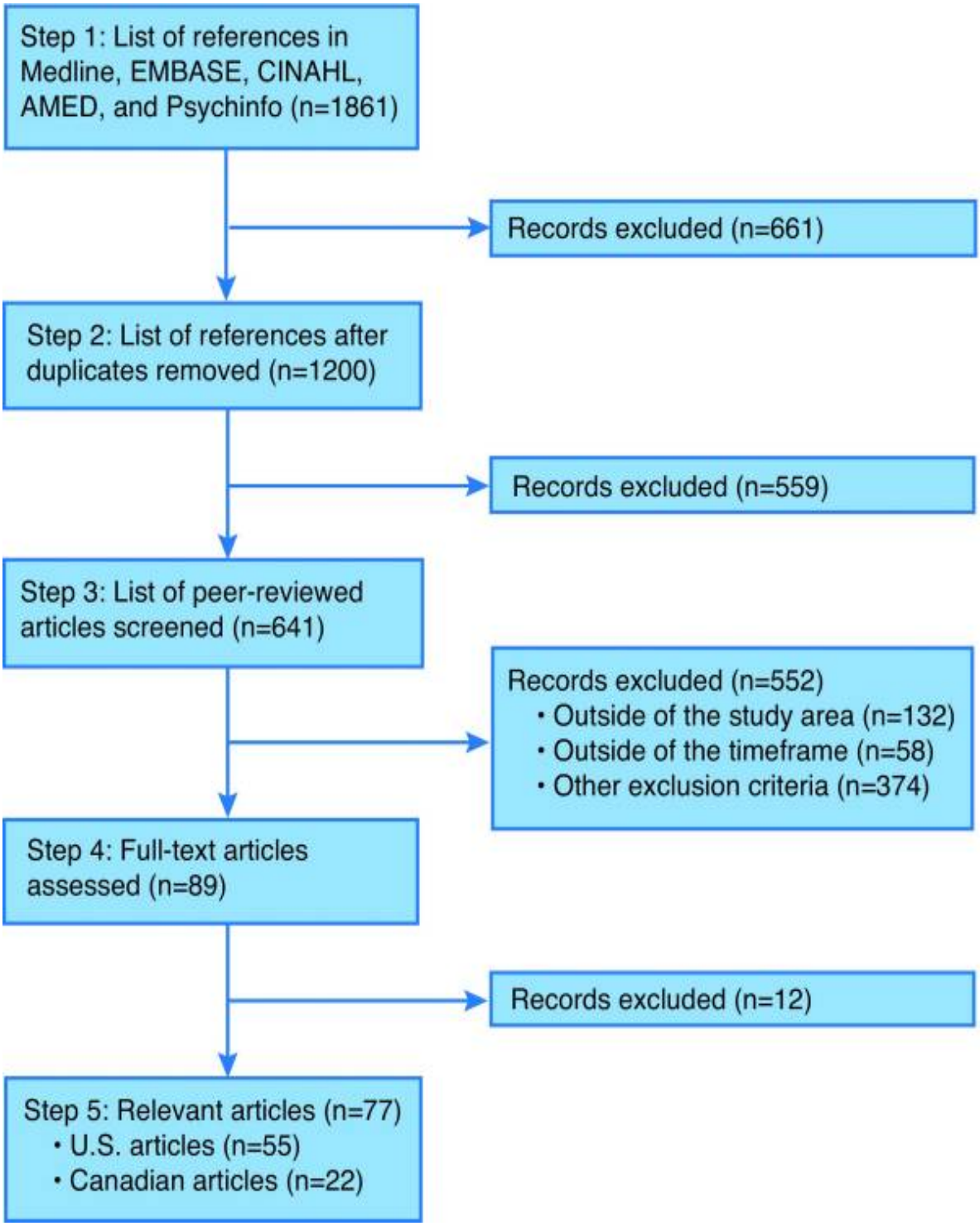

Figure 6.1. Methodology of identifying relevant studies for the scoping review and the results at each step.

Figure 6.2. Word cloud showing the most frequent words appearing in the titles and abstracts of the articles.

Associated with the second highest eigenvalue, the PCA grouped age, income, race, insurance coverage and location where they live as another overarching factor. These socioeconomic/demographic characteristics pertain to patient-level information. From the word cloud (Figure 6.2), topics including “age”, “African American”, “Caucasian”, “education”, and “demographic” emerged, which are complimentary to the identified socioeconomic/demographic characteristics.

Similarly, regarding the third highest eigenvalue, the PCA grouped six different reasons for treatment choice as a third overarching factor (see Table 6.3 for the list of topics under this factor). These reasons pertain to patient-level reasons for choosing or avoiding a treatment

option. Based on the word cloud, topics including “side effects”, “time”, “aid”, “months”, and “personal” emerged, which are complimentary to this identified key factor.

With respect to the fourth highest eigenvalue, the PCA grouped factors pertaining to patients’ psychological experiences during the LPC treatment decision-making process (before and after the decision) as a fourth overarching factor. The topics within this factor include uncertainty faced by patients before the treatment or regret/satisfaction of the decision after the treatment (see Table 6.3 for other topics within this factor). The list of words including “regret”, “satisfaction”, “conflict”, “quality-of-life”, “uncertainty”, “determined”, and “impact” in the word cloud are related to the psychology of treatment decision experience.

Lastly, the PCA grouped the topics associated with the level of involvement for patients, their families, friends and the healthcare providers as a fifth overarching factor. There were several topics within the word cloud strongly suggestive of the topics associated with the roles in LPC treatment decision-making process, including “influence”, “physician”, “urologist”, “partners”, “considered”, “consultation”, “role”, “knowledge”, “control”, “support” and “involvement”.

6.4. Discussion

The PCA computed eigenvalues for each factor. These eigenvalues are a measure of the amount of variation in the information collected from the relevant articles regarding decision-making themes: the higher the eigenvalue, the more frequently articles expressed topics associated with the factor. The eigenvalues do not provide information on the level of importance of the factors. For example, the factor “treatment type” (as discussed later) had the highest eigenvalue in the PCA, which does not imply it is the most important LPC treatment decision-making factor. In general, a factor having a higher eigenvalue does not imply it is more important than factors with lower eigenvalues.

Based on these eigenvalues, our analysis identified five factors commonly studied regarding LPC treatment decision-making, including treatment type, patient socioeconomic/demographic characteristics, personal reasons of patients, psychological factors, and involvement level within the decision-making process. While the scoping review results

cannot be used to determine the importance of each of these factors, we hypothesize that they influence LPC treatment decision-making.

Regarding how treatment type may be involved in LPC treatment decision-making, some research suggest patients prefer surgery or radiation therapy due to the perception level regarding side effects and perceived treatment invasiveness (12, 14-16, 50, 60, 62). Patients tend to prefer information on side effects or survival, which are different for each treatment type (38, 82, 90). Other work suggests patients might avoid invasive treatments or choose complementary alternative medicine (CAM) or AS/WW because: (i) they prefer to avoid the side effects of curative treatments; (ii) they are waiting for improvements in curative treatment options; and (iii) they perceive curative treatments to be inconvenient or a burden (9, 11, 13, 33, 34, 73).

In terms of how socioeconomic/demographic characteristics contribute, some research studied the roles that age, race, income, education, type of insurance coverage and where one lives might have in LPC treatment decision-making (10, 14, 23, 26, 35, 53, 54, 58). For example, African-Americans with high risk LPC in the United States are less likely to receive treatment than Caucasians (91, 92). Other research suggests the availability of insurance can reduce these racial disparities (91, 92). Some patients not undergoing any treatment within six months of diagnosis were more likely to be older age (over 75), non-Caucasians and living in areas with fewer urologists (54).

Personal reasons for a LPC treatment decision include survival probability, urinary function, rectal function, and ability to work (38, 82, 90). Some of the articles in this review contained decision aid tools available for educating patients about these personal reasons and assisting patients in making informed decisions (36, 57, 72, 74, 75, 79, 83, 84).

Psychological experiences are a fourth factor that the PCA identified. These experiences include such things as feelings of stress, regret, uncertainty and questions regarding quality of life (27, 30, 35, 61, 66). There were reports of decisional regret among men with treatment side effects such as sexual, bowel or urinary dysfunction (27, 30, 35, 61, 66). Patients, who felt they were poorly informed or were not prepared enough regarding their treatments, were reported to have increased risk of regrets and psychological distress (13, 27, 32, 35, 36, 39, 46, 61, 66, 68,

69, 72, 81, 93). Men who were more actively involved in the decision-making and had greater knowledge of LPC were less likely to report decisional stress and had higher satisfaction.[64]

The last factor identified by the PCA was level of patient involvement. Some LPC patients prefer an active or collaborative role with their physician in their treatment decision-making (13, 15, 23, 24, 29, 71, 77, 84, 86, 87). When health care providers included patients in the treatment decision-making process, patients reported higher levels of satisfaction (88). Further, when patients discussed their treatment with physicians, families and friends, they reported an improved state of mind and ability to cope with their cancer diagnosis (49).

Assessing the importance of each of the factors is needed because of their implications for improving patient decision-making experience and healthcare provider knowledge. Further studies are needed to identify the role, if any, that each of these factors have in LPC treatment decision-making. Further studies are also needed to see how the five factors interact with each other in shaping the LPC decision-making experience for patients. For those factors found to influence LPC treatment decision-making, interventions and policies could be developed to improve the decision-making experience for patients.

6.5. Conclusions

Our review identifies that there are five factors common to the LPC treatment decision-making literature: treatment type, socioeconomic/demographic characteristics of the patients, personal reasons of patients, psychological factors, and level of involvement in the decision-making process. Our study provides a basis for future research identifying the importance of each factor, and how they interact with each other in shaping the LPC treatment decision-making experience for patients. This future research has the potential to inform interventions and improve the LPC treatment decision-making experience for patient care.

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CHAPTER 7 – CONCLUSIONS

Overall, this work addressed two objectives. First, we determined associations between components of healthcare access and each of PCa incidence, treatment usage and time-to-treatment trends among Saskatchewan patients. Second, we identified and described the overarching themes influencing treatment decision-making for localized PCa patients.

To address the first objective, in Chapters 3, 4 and 5, we explored the following research questions respectively: (1) "Is the PCa incidence in Saskatchewan affected by changes in family physician density, the remoteness level of where a patient lives, and the closest PCa assessment centre from where a patient lives?"; (2) "Are the PCa treatment utilization rates in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?"; and (3) "Are the PCa time-to-treatment outcomes in Saskatchewan affected by changes in the remoteness level of where a patient lives and the closest PCa assessment centre from where a patient lives?". To address the second objective, in Chapter 6 we explored the following research question: "What factors and corresponding themes in the literature have been identified to affect the treatment decision-making of localized prostate cancer patients in Canada and the United States?".

7.1. Summary of Findings

In Chapter 3 we showed that disparities in PCa outcomes were associated with where patients live, including a higher than expected incidence of metastatic PCa in northern/central portions of Saskatchewan. In this chapter, we also showed a higher than expected incidence of intermediate-risk and low-risk PCa in the areas proximal to the city of Regina. In addition, we showed a negative association between physician density and standardized incidence ratio for metastatic PCa and high risk PCa. Hence higher physician density regions had lower than expected standardized incidence ratios for metastatic PCa and high risk PCa. The location where patients live and physician density could be viewed, respectively, as the accessibility and availability components of healthcare access factors as described by Penchansky and Thomas (1). Hence Chapter 3 illustrates the possible impact that healthcare access factors (location where patients live and physician density) may have on PCa outcomes, including geographic diagnosis patterns (standardized incidence ratios) in Saskatchewan.

In Chapter 4, we found that healthcare access factors including where patients live, remoteness level (urban and rural areas) and closest PCa assessment centre to a geographic area (GA) were associated with PCa treatment choices in Saskatchewan. Living in rural areas was negatively associated with choosing surgery compared to patients living near the major centres of Saskatoon and Regina. Those patients whose closest PCa assessment centre was Saskatoon had higher odds of undergoing radiation therapy treatment compared to Regina. In addition, those patients whose closest PCa assessment centre was Regina had higher odds of choosing active surveillance/watchful waiting compared to Saskatoon. Overall, healthcare access factors (where patients live, GA remoteness index and closest PCa assessment centre to a GA) were associated with PCa treatment choice (surgery, radiation therapy and active surveillance/watchful waiting) for patients in Saskatchewan. The location where patients live, GA remoteness index and closest PCa assessment centre to a GA possibly fall within the accessibility spectrum of healthcare access factors (1). Hence Chapter 4 showed the possible impact that healthcare access factors (GA remoteness index, location where patients live and closest PCa assessment centre to a GA) may have on PCa treatment choice in Saskatchewan.

In Chapter 5, we showed that patients who live in remote regions in Saskatchewan had, on average, longer time-to-treatment outcomes for radiation therapy (specifically from date of diagnosis to start of radiation therapy treatment). In addition, this study found that time-to-treatment outcomes were, on average, longer in areas with Saskatoon as the closest PCa assessment centre. Hence both healthcare access factors (GA remoteness index and closest PCa assessment centre to a GA) possibly impact PCa time-to-treatment outcomes in Saskatchewan.

Chapter 6 identified five factors common to the localized PCa treatment decision-making literature: treatment type, socioeconomic/demographic characteristics of the patients, personal reasons of patients, psychological factors, and level of involvement in the decision-making process. Because these factors might influence localized PCA treatment decision-making, they could be further explored to improve PCa treatment making interventions and policies for patients.

7.2. Discussion and Policy Implications

In this doctoral research, we showed geographic disparities exist in PCa incidence (Chapter 3), PCa treatment choice (Chapter 4) and PCa time-to-treatment outcomes (Chapter 5) in Saskatchewan. In addition, the work presented in Chapter 6 identified additional factors that might influence PCa decision making. Healthcare access factors, including location of patients, closest PCa assessment centre to a GA, GA remoteness index and physician density, were studied and identified to possibly impact PCa outcomes.

The work in Chapter 3 shows the possible impact of healthcare provider availability on PCa outcomes, including the negative association between physician density and standardized incidence ratio for metastatic PCa and high risk PCa. In the literature, similar trends were found in the United States where availability of healthcare providers was negatively associated with incidence of late-stage diagnosis of PCa (2). Similar to the United States, we found in our study that PCa outcomes in Saskatchewan may be facing issues associated with availability of healthcare providers. Previous studies have shown the positive impact of increasing physician density on health outcomes (3-9). Hence, given the findings in Chapter 3, implementing policies addressing the adequate supply of healthcare providers, including availability of family physicians, might improve cancer outcomes in Saskatchewan.

In Chapter 3, physician availability was negatively associated with the standardized incidence ratio for metastatic PCa and high risk PCa. This geographic trend in PCa incidence could possibly be due to physician practice differences in Saskatchewan, including differences in PCa screening practices among physicians (10). Historical PCa screening trends in Saskatchewan suggest incidence of PCa in Saskatchewan were possibly influenced by the usage of PCa screening tests (11, 12). In addition, it is known in the literature that decrease in PCa screening may possibly increase the incidence of advanced staged PCa (13). Therefore, physician practice variation including PCa screening usage might possibly explain the geographic trends in PCa diagnosis rates in Saskatchewan. Possible policy implications of addressing PCa screening may include government programs exploring other PCa screening methods, including urine-based tests and advanced prostate health index blood tests, as options provided to rural clients (14). The findings from Chapter 3 show the significance of addressing the pattern of late diagnosis of PCa

cases in north-eastern parts of Saskatchewan and addressing the possible associated healthcare access issues in the areas, including physician practice.

The work in Chapter 4 shows the possible impact of healthcare provider accessibility on PCa treatment choice, including the negative association between living in rural/remote regions and choosing surgery for PCa treatment. The findings in Chapter 4 suggest that rural dwellers in Saskatchewan might be choosing PCa treatment differently than urban dwellers. In the literature, we found a similar trend in parts of United States and Australia where living in rural areas was associated with a lower likelihood to undergo PCa surgery (15-20). In the literature, possible reasons associated with treatment choice among rural dwellers were travel time, distance, availability of specialist appointments, and rural culture, including feeling like an outsider in city centres and less willingness to seek care in distant cities (21-23). These possible reasons, including travel to city hospitals may mean additional cost for the patients when seeking treatment, hence if similar reasons influence Saskatchewan patients living in rural areas, policy changes to address these disparities might include exploring reimbursement of travel and accommodation for PCa patients living in rural/remote areas in Saskatchewan (24). Therefore, based on the findings in Chapter 4, possibly offsetting the cost related to travel and financial loss might reduce the disparity in treatment trends among rural/remote patients in Saskatchewan (24).

In Chapter 4, treatment utilization patterns were associated with changes in the remoteness level of patients and the closest PCa assessment centre to where patients live. We found usage of active surveillance/watchful waiting treatment was most common among older age and low-risk PCa patients. Based on the treatment guidelines, active surveillance/watchful waiting treatment would be recommended for patients with less than 10 years of life expectancy and those with low-risk PCa (25-27). Hence, Chapter 4 shows that the usage of active/watchful waiting treatment in Saskatchewan was consistent with the expected clinical treatment guidelines (25-27). For hormonal therapy, those with metastatic PCa were commonly receiving the treatment in Saskatchewan. The most common use of hormonal therapy among metastatic PCa patients aligns with the clinical treatment guidelines and shows Saskatchewan trends for hormonal therapy were consistent with what we may expect based on treatment guidelines (25-27). The most common usage of radiation therapy and surgery among intermediate and high risk PCa patients was also consistent with the treatment guidelines (25-27). In addition, Chapter 4

shows radiation therapy was commonly used with hormonal therapy, which is expected based on the treatment guidelines (25-27). Overall, the treatment usage results by risk levels in Chapter 4 were aligned with the expected clinical treatment guidelines (25-27).

In Chapter 4, the treatment utilization patterns of patients living in the rural/remote areas and receiving radiation therapy treatment depended on the closest treatment centre for the patients (i.e., the interaction between remoteness index and closest PCa assessment centre). We found that patients had higher odds of receiving radiation therapy if their closest PCa assessment centre was Saskatoon compared to Regina (for both rural and urban areas). We also found that for those patients whose closest assessment centre was Regina, urban patients had a higher odds of receiving radiation therapy than rural patients. While we expected to see the same urban-rural disparity for radiation therapy treatment utilization in the Saskatoon area, we did not find this. Hence possible reasons for the differences between the Saskatoon and Regina areas need to be explored.

Combining the work from Chapters 3 and 4, we found that the geographic location of patients (the accessibility component of healthcare access factors) was associated with PCa outcomes, including PCa SIRs (Chapter 3), and treatment choice (Chapter 4). Lower than expected incidence for low-risk PCa was found in the north-western part of Saskatchewan (Chapter 3), and the same surrounding areas had lower than expected utilization odds for active surveillance/watchful waiting (Chapter 4), which were complementary results because active surveillance/watchful waiting was more commonly utilized among low-risk PCa patients (Chapter 4). In terms of policy implications, geographic variation in low-risk PCa and utilization of active surveillance/watchful waiting could be indicative of a physician practice variation in diagnostic and treatment care within Saskatchewan; hence areas with lower than expected low-risk PCa incidence and a lower odds of choosing active surveillance/watchful waiting may have differing PCa screening/diagnosis and active surveillance/watchful waiting practices, respectively, than other parts of Saskatchewan. Hence, the role of physician practice and availability of physicians might have impacted PCa outcomes in Saskatchewan.

The work in Chapter 5 shows associations between healthcare provider accessibility on PCa time-to-treatment outcomes, including the positive association between living in rural/remote regions and time from diagnosis to radiation therapy treatment. In the literature, we

only found a similar trend for other types of cancers including lung and colorectal in studies from Australia (28, 29). Hence, the findings in Chapter 5 were unique to PCa treatment literature and it shows that rural dwellers in Saskatchewan might delay their PCa treatment due to where they live. Similar to Chapter 4, the possible reasons for these findings are travel time, distance, availability of specialist appointments, and rural culture including preference to stay closer to home for treatment and not preferring large city centres for seeking treatment (21-23). The need for travel to seek treatment may have associated costs, including commuting costs and accommodations for the patients and possibly their families (24). Hence, since there may be a cost due to travel or possible loss of income due to travel time from rural areas, policies of reimbursing travel similar to Chapter 4 discussed in the previous paragraph could be explored as a means to possibly reduce the disparity in treatment delay trends among rural/remote patients in Saskatchewan (24).

In Chapter 5, we found that the time-to-treatment from 'ready-to-treat' dates were longer for areas near Saskatoon when compared to areas near Regina, specifically among the low risk and intermediate risk patients (interaction effect between risk levels and closest PCa assessment centre). Among the high-risk patients, there were no differences between the areas near Saskatoon and Regina. A possible reason could be due to potential differences in the interpretation of how 'ready-to-treat' date is assigned in each of the centres and/or differences in the patient volumes in the two centres (Saskatoon and Regina). Understanding if these are possible explanations requires further research. In addition, we found the time-to-treatment from 'ready-to-treat' date periods to be shorter for clients having additional treatments, which requires further exploration and research at the treatment centres, including analysis of the patient flow at the treatment centres.

In Chapter 5, the average wait for PCa radiation in Saskatoon and Regina were less than 3 weeks. During the study period (2010 to 2014), the target wait period set was 3 weeks for 90% of the patients receiving radiation therapy including PCa patients (based on communication with Saskatchewan Cancer Agency). However, Chapter 5 shows that 90^{th} percentile radiation therapy wait period was 5 weeks, which is 2 weeks longer than the target wait period. Based on the findings of Chapter 5, further measures may be needed to reduce the wait period between 'ready-to-treat' date and initial radiation therapy for PCa patients, including addressing any physician

availability at Saskatoon and Regina treatment centres (based on communication with Saskatchewan Cancer Agency). Further research to assess the impact of increasing physician availability, staffing levels, and patient flow on time-to-treatment outcomes should be explored using dynamic simulation modelling to potentially identify system levels interventions, including standardization of patient flow at treatment centres in order to improve time-to-treatment outcomes.

Combining the work from Chapters 4 and 5, we found that the closest PCa assessment centre to a GA (accessibility component of healthcare access factors) were found to be associated with choice of PCa treatment and treatment delays. For radiation therapy, those patients whose closest PCa assessment centre was Saskatoon had greater odds of choosing radiation therapy (Chapter 4) and had a longer waiting time for radiation therapy treatment compared to patients whose closest PCa assessment centre was Regina (Chapter 5). Areas with higher odds of choosing radiation therapy had lower odds of choosing active surveillance/watchful waiting (Chapter 4). These regional disparities between Saskatoon and Regina in treatment patterns could be due to differing physician practices as observed in other studies where physician advice could strongly influence the final treatment decision for PCa patients (30-32). The work in Chapters 4 and 5 showed regional disparities in treatment outcomes between Saskatoon and Regina, and the regional disparities may be due to differences in care practices between Regina and Saskatoon. Policies informing standardized care between Saskatoon and Regina in terms of wait time and treatment delays should be explored.

The work in Chapter 6 identified possible additional factors that could affect PCa treatment decision, including treatment type, socioeconomic/demographic characteristics of the patients, personal reasons of patients, psychological factors, and level of involvement in the decision-making process. In terms of choosing or avoiding certain treatment types, patients could be influenced by their perceptions of treatment performance and side effects (33-39). Hence, policies involving decision aids to assist treatment decision-making could possibly reduce the uncertainties faced by patients (40-47). Socioeconomic/demographic disparities in choosing treatment were identified, including the role of income (33, 48-54). Financial hardship among cancer patients in Canada is known to be an issue and, if similar issues among PCa patients in Saskatchewan exist, policies to address the loss of income for cancer patients should be explored

(24). One possible gap in the Canadian literature was the reference to experiences on Indigenous peoples for PCa treatment decision making. Personal reasons for choosing a treatment included the avoidance of certain side effects of treatments including sexual function and the ability to make decisions in their preferred timeline (55, 56). Similar policy consideration of involving decision aids to assist treatment decision-making could possibly improve patient satisfaction with their treatment decision making journey (33-39). In terms of psychological factors, patients may face stress due to lack of information sharing by their healthcare provider (41, 42, 51, 57-67). Hence, possible mechanism and policy to improve the patient decision making experience would need involvement of patients in the decision-making process (68). Research shows active participation of patients in treatment decision-making had a positive impact on their cancer management process (69). Hence, policies should be explored to improve the patient treatment decision making process, including decision aids, to address any patient financial barriers and facilitate shared decisions with the care providers.

The findings from the international literature, including developed and developing countries, highlight the significance of expanding primary care availability in rural areas as a mechanism to reduce urban/rural disparities, due to the role of primary care in disease prevention, early detection of disease, and reducing mortality (70, 71). Expanding primary care in rural areas allows for better coordinating with other health services to improve the quality of life for patients (70, 71). Other common issues for rural areas include addressing barriers associated with travel and loss of income when seeking care, hence policies to reimburse travel and accommodation should be explored as possibilities to help address the rural disparities in PCa outcomes (24, 70, 71).

The potential limitations of this doctoral research, include the PCa incidence patterns in Chapter 3 may have been influenced by the availability of urologists. This limitation suggests the need for further research exploring the role of urologists in the PCa diagnosis patterns, including a sensitivity analysis to address the possible impact of urologist density on PCa incidence. In Chapter 4, due to gaps in the available data, those we identified as receiving active surveillance/watchful waiting may have included individuals whose PCa was unmanaged. To determine what proportion of patients had unmanaged PCa and what proportion were being actively surveilled, we suggest conducting chart reviews to address this limitation. In Chapter 4,

note our term “treatment choice” that we used to describe a treatment utilization pattern may not necessarily reflect an informed choice of a patient to choose a certain PCa treatment. In Chapter 5, because of gaps in the available data, our term “delays” may include patient or system-based factors possibly impacting the longer time-to-treatment.

7.3. Conclusions

This doctoral research explored the possible reasons for the high mortality rates in Saskatchewan, when compared to other provinces. To explore the possible reasons for the adverse PCa survival outcomes in Saskatchewan, this work assessed two study objectives: (1) determining any associations between components of healthcare access and each of PCa incidence, treatment usage and time-to-treatment trends among Saskatchewan patients; and (2) identifying common factors influencing PCa treatment decision-making. Healthcare access factors, including location of patients, closest PCa assessment centre, remoteness and physician density, were studied and identified to possibly impact PCa outcomes. The work in Chapter 3 showed the association between healthcare provider availability and PCa diagnosis patterns and, consequently, identified the possible need for an adequate supply of healthcare providers to improve cancer outcomes. The work in Chapters 4 and 5 showed the possible impact of healthcare accessibility on PCa treatment choice and delays, and therefore, identified the possible need for equitable policies to address urban/rural disparities in assisting patients with their treatment outcomes in Saskatchewan. The work in Chapter 6 informed future research to improve the treatment decision-making experience for PCa patients. Overall, this doctoral work identified the possible impact of healthcare factors on PCa outcomes, which may influence the adverse PCa outcomes in Saskatchewan, and the work identified factors that may further influence treatment decision-making.

This doctoral research identifies the possible need for improving physician availability in Saskatchewan with an equitable geographic distribution of primary care providers to support early detection of PCa. Such policies may include improved access to specialty care based on the recommendations of Canadian Medical Association through streamlining patient flow, including standardized referral processes and physician practices (72). Other possible policies may include

expanding primary care, compensating patients for travel time, and additional investments in rural based treatment centres (24, 70, 71).

7.4. Future Research Areas

Based on the findings of Chapter 3, further research is needed to explore whether physician practice variation might be influencing the diagnosis patterns in Saskatchewan. Additional research to explore the role of urologist practice and availability may provide further insight in the PCa diagnosis patterns in Saskatchewan. In addition, further research is needed to identify the reasons for the clustering of higher incidence for early-stage PCa near the city of Regina and the clustering of late-stage PCa near the city of Saskatoon. Further research should be conducted to explore the role of healthcare access in northern Saskatchewan for PCa incidence, treatment utilization and time-to-treatment given the unique demographic with over 85% of the population identifying as Indigenous (compared to 16% of the overall Saskatchewan population) and comprising of 'fly-in' communities. This research should include a sensitivity analysis using historical Saskatchewan Cancer Registry data to identify the possible impact of excluding northern Saskatchewan (due to the small cell size per outcome) from the analyses presented in this doctoral work.

Computer simulation modelling that includes the latent progression of the PCa risk levels should be explored to account for disease progression and to improve estimates of undiagnosed late stage PCa cancer in Saskatchewan. Based on the findings of Chapter 4, further research is needed to explore whether rural access barriers including cost of travel, accommodation, financial factors and rural cultural components influence treatment decision patterns in Saskatchewan. In addition, further research is needed to identify the reasons for higher odds of radiation therapy in among patients whose closest PCa assessment centre is Saskatoon compared to Regina. It is not known why patients in rural areas have lower odds of undergoing surgery and further research is needed to identify the underlying reasons among rural dwellers in Saskatchewan. For active surveillance/watchful waiting, a possible chart review of client records should be explored to estimate the true prevalence of using active surveillance/watchful waiting among PCa patients in Saskatchewan.

Based on the findings of Chapter 5, further research is needed to identify whether differences in care practice exist between Regina and Saskatoon and if it has any contributions to the longer waits in Saskatoon compared to Regina. This includes exploring reasons for shorter time to treatment from "ready-to-treat" date for clients using additional treatments. Based on the findings of Chapter 6, further research is needed to explore if the additional factors identified affect treatment decision-making among PCa patients in Saskatchewan. Further research is needed to identify the importance of each of the treatment decision-making factors in Saskatchewan. Lastly, research is needed as to whether the regional disparities in treatment outcomes (example, treatment delay) identified in Chapters 4 and 5 could be further impacted by the factors identified in Chapter 6. In addition, future research may also focus on exploring the changes in policies in the recent period between 2015 and 2021 in Saskatchewan compared to the baseline data from the study period (2010 to 2014) for each of the PCa outcomes, and assess the impact of recent cancer diagnosis and treatment policies on healthcare access in rural Saskatchewan. The findings of this doctoral work could be further translated to policy makers and stakeholders through presentations to the knowledge users, including Saskatchewan Medical Association, Saskatchewan Cancer Agency, Saskatchewan Health Authority, Saskatchewan Ministry of Health and organizations dedicated to improving health in rural and remote areas, including Indigenous organizations. Further research should be explored with other research centres related to chronic condition areas on healthcare access through presentations in the provincial, national and international conferences. The findings of this research would provide opportunities to explore whether healthcare access factors possibly impact other cancers, and chronic disease conditions in Saskatchewan.

7.5. References

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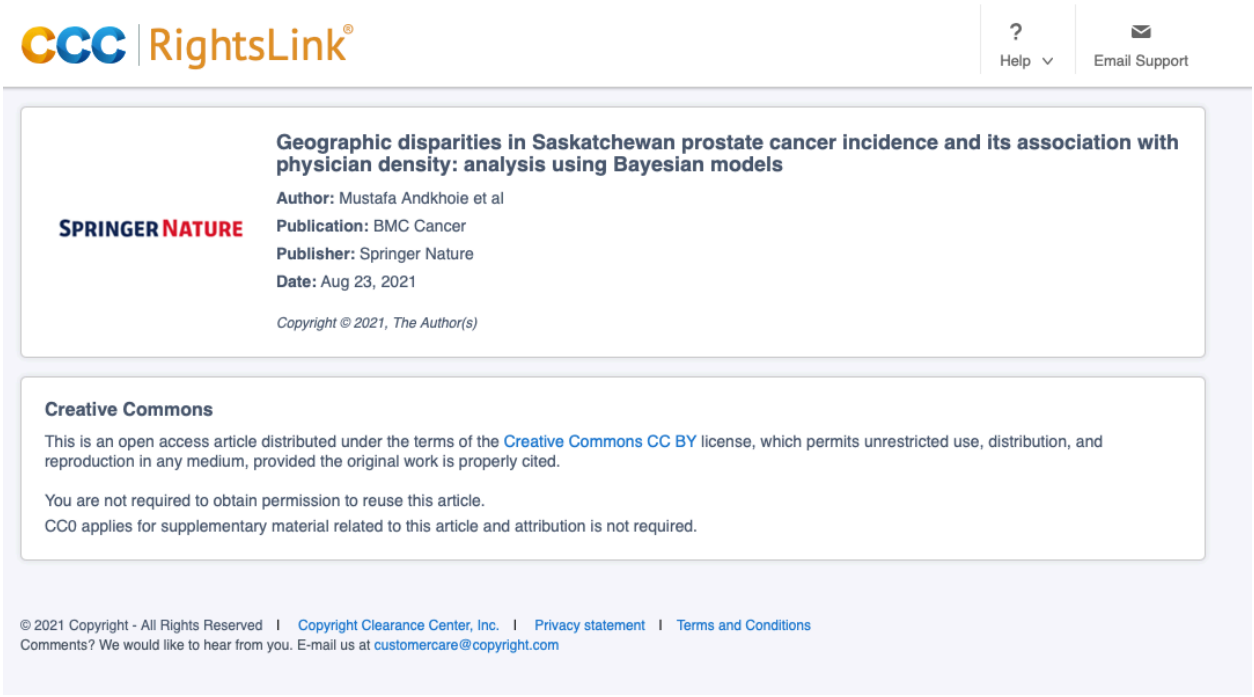

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ORIGINAL REVIEW DATE	APPROVED ON	APPROVAL OF	EXPIRY DATE
18-Feb-2015	10-Mar-2015	Amended Application to Access Existing Health Data for Research submitted March 5, 2015 Acknowledge receipt of: McMaster certificates for Mustafa Andkhoie, Cheryl Waldner and Michael Szafron	09-Mar-2016

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The study is acceptable on scientific and ethical grounds. The Bio-REB considered the requirements of section 29 under the Health Information Protection Act (HIPA) and is satisfied that this study meets the privacy considerations outlined therein. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face) meeting. If a protocol has been reviewed at a full board meeting, a subsequent study of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://research.usask.ca/for-researchers/ethics/index.php.

REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval

Please send all correspondence to:

Research Ethics Office
University of Saskatchewan
Box 5000 RPO University
1607 – 110 Gymnasium Place
Saskatoon, SK Canada S7N 4J8

UNIVERSITY OF SASKATCHEWAN Biomedical Research Ethics Board (Bio-REB)

Certificate of Re-Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Cheryl Waldner	Large Animal Clinical Sciences	15-34

INSTITUTION (S) WHERE RESEARCH WILL BE CARRIED OUT

Saskatchewan Cancer Agency
4101 Dewdney Avenue
Regina SK S4T 7T1

SUB-INVESTIGATOR(S)

Michael Szafron

STUDENT RESEARCHER(S)

Mustafa Andkhoie

FUNDER(S)

INTERNALLY FUNDED

TITLE:

Are there Regional Differences in the Rate and Severity of Prostate Cancer Cases in Saskatchewan?

RE-APPROVED ON	EXPIRY DATE
03-Feb-2016	02-Feb-2017

Full Board Meeting ☐

Delegated Review ☑

CERTIFICATION

The study is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This re-approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Biomedical Research Ethics Board reviews above minimal studies at a full-board (face-to-face meeting. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project. For more information visit http://www.usask.ca/research/ethics_review/.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. This re-approval and the views of this REB have been documented in writing.

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB)

Certificate of Re-Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	Bio #
Michael Szafron	School of Public Health	15-34

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT
Saskatchewan Cancer Agency
4101 Dewdney Avenue
Regina SK S4T 7T1

STUDENT RESEARCHER(S)
Mustafa Andkhoie

FUNDER(S)
UNIVERSITY OF SASKATCHEWAN

TITLE: Timeliness and predictors of prostate cancer in Saskatchewan: A Comprehensive epidemiological Review

RE-APPROVED ON	EXPIRY DATE
03-Jan-2018	02-Jan-2019

Delegated Review ☒ Full Board Meeting ☐

IRB 1 Registration #00001471 ☐ IRB 2 Registration #00008358 ☐ Not Applicable ☒

CERTIFICATION
The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named research study. The study was found to be acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research study, and for ensuring that the authorized research is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved protocol or consent process.

FIRST TIME REVIEW AND CONTINUING APPROVAL
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REB ATTESTATION
In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2 2014).

UNIVERSITY OF SASKATCHEWAN

Certificate of Re-Approval

Ethics Number: 15-34

Principal Investigator: Michael Szafron Department: School of Public Health

Locations Where Research Activities are Conducted: Saskatchewan Cancer Agency, Canada

Student(s): Mustafa Andkhoie

Funder(s): Saskatchewan Cancer Agency
University of Saskatchewan

Sponsor:

Title: Timeliness and predictors of prostate cancer in Saskatchewan: A Comprehensive epidemiological Review

Protocol Number:

Approved On: 10/01/2019

Expiry Date: 09/01/2020

Acknowledgment Of: N/A

Review Type: Delegated Review

IRB Registration Number: Not Applicable

* This study, inclusive of all previously approved documents, has been re-approved until the expiry date noted above

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project.The project is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved project.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Research Ethics Boards review above minimal projects at a full-board (face-to-face) meeting. If a project has been reviewed at a full board meeting, a subsequent project of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2014).

Digitally Approved by Gordon McKay, Ph.D.
Chair, Biomedical Research Ethics Board
University of Saskatchewan

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB) 19-Dec-2019

Certificate of Re-Approval

Ethics Number: 15-34

Principal Investigator: Michael Szafron Department: School of Public Health

Locations Where Research Activities are Conducted: Saskatchewan Cancer Agency, Canada

Student(s): Mustafa Andkhoie

Funder(s): Prostate Cancer Fight Foundation
Saskatchewan Cancer Agency
University of Saskatchewan

Sponsor:

Title: Timeliness and predictors of prostate cancer in Saskatchewan: A Comprehensive epidemiological Review

Protocol Number:

Approved On: 19/12/2019

Expiry Date: 18/12/2020

Acknowledgment Of:

Review Type: Delegated Review

IRB Registration Number: Not Applicable

* This study, inclusive of all previously approved documents, has been re-approved until the expiry date noted above

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project.The project is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved project.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Research Ethics Boards review above minimal projects at a full-board (face-to-face) meeting. If a project has been reviewed at a full board meeting, a subsequent project of the same protocol may be reviewed through the delegated review process. Any research classified as minimal risk is reviewed through the delegated (subcommittee) review process. The initial Certificate of Approval includes the approval period the REB has assigned to a study. The Status Report form must be submitted within one month prior to the assigned expiry date. The researcher shall indicate to the REB any specific requirements of the sponsoring organizations (e.g. requirement for full-board review and approval) for the continuing review process deemed necessary for that project.

REB ATTESTATION

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Digitally Approved by Gordon McKay, Ph.D.
Chair, Biomedical Research Ethics Board
University of Saskatchewan

UNIVERSITY OF SASKATCHEWAN

Biomedical Research Ethics Board (Bio-REB) 02-Dec-2020

Certificate of Re-Approval

Ethics Number: 15-34

Principal Investigator: Michael Szafron Department: School of Public Health

Locations Where Research Activities are Conducted: Saskatchewan Cancer Agency, Canada

Student(s): Mustafa Andkhoie

Funder(s): Prostate Cancer Fight Foundation
University of Saskatchewan

Sponsor:

Title: Timeliness and predictors of prostate cancer in Saskatchewan: A Comprehensive epidemiological Review

Approval Effective Date: 18/12/2020

Expiry Date: 18/12/2021

Acknowledgment Of: None

Review Type: Delegated Review

IRB Registration Number:

* This study, inclusive of all previously approved documents, has been re-approved until the expiry date noted above

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project.The project is acceptable on scientific and ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period provided there is no change to the approved project.

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REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations and carries out its functions in a manner consistent with Good Clinical Practices. Members of the Bio-REB who are named as investigators, do not participate in the discussion related to, nor vote on such studies when presented to the Bio-REB. This approval and the views of this REB have been documented in writing. The University of Saskatchewan Biomedical Research Ethics Board is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 2018).

Digitally Approved by Dr. Gordon McKay, Ph.D.
Chair, Biomedical Research Ethics Board
University of Saskatchewan